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## HEALED SUBACUTE BACTERIAL ENDOCARDITIS

PHILIP ROSENBLATT, MD, AND LEO LOEWE, MD  
BROOKLYN

Evidence for the statement that patients with subacute bacterial endocarditis may recover has hitherto been the fact that those with a typical clinical picture and from whose blood organisms are grown on cultures do survive and become free from symptoms and bacteria<sup>1</sup> Libman<sup>2</sup> reported at least 3 per cent of recoveries in the usual type of the disease. He was also convinced that many more recoveries occur in persons with a mild form of the disease which is often overlooked.

Pathologic confirmation of healed subacute bacterial endocarditis is, however, largely indirect and inferential in nature. For example, Weiss and Rhodes<sup>1</sup> examined a group of hearts obtained at autopsy and selected 3 as being examples of completely healed subacute bacterial endocarditis. Others are described as suggesting a "healing" endocarditis. Hamman<sup>3</sup> similarly described 4 cases, 2 of which showed evidence of "almost complete healing of vegetations," while in the other 2 the cardiac lesions were of such a nature as to strongly imply a healed bacterial endocarditis rather than valves damaged by the rheumatic process.

It is not within the province of this report to enter into a discussion of what Libman terms "recurrent mild cases," or into the vagaries of the "bacteria-free" stage of the disease. Most observers are agreed that the clinical course of subacute bacterial endocarditis is often erratic. On the other hand, they do not share Libman's opinions and look on classic cases with gloomy prognosis.

With the newer methods of therapy, reports of clinical cures have become more frequent. How-

ever, the dearth of pathologic confirmation still persists. It is the purpose of this report to correct partially this disproportion between clinical observation and pathologic proof. The following cases are examples of classic subacute bacterial endocarditis cured by the method of combined penicillin-heparin therapy<sup>4</sup>. Both patients later experienced congestive heart failure due to excessive valvular damage and finally came to autopsy.

CASE 1—J. K. was a white woman, aged 33. The diagnosis had been established as subacute bacterial endocarditis, and the patient was transferred from the Hospital for Joint Diseases to the Jewish Hospital in Brooklyn on Nov. 9, 1943 for penicillin-heparin therapy. There was no past history of rheumatic fever or chorea. Her illness dated back seven months to a period marked by fever and malaise. Laboratory and clinical evidence prior to her admission included cultures of the blood positive for *Streptococcus viridans* on several occasions, crops of white-centered petechiae, a palpable spleen, moderate secondary anemia and cardiac murmurs. She had been seen in consultation by Dr. E. Libman, who concurred in the diagnosis. Prior to her admission to the Jewish Hospital she was treated with massive doses of sulfadiazine by the intravenous route. These were ineffectual. During the period of sulfonamide therapy sudden severe costovertebral pain on the right side, tenderness and hematuria developed, after which the kidney became palpable. The kidney gradually increased in size reaching to the crest of the ilium. Sulfadiazine levels in the blood ranged from 36 to 98 mg per hundred cubic centimeters without sterilizing the blood stream.

On admission to this hospital she appeared euphoric and chronically ill. There was a harsh, short, systolic murmur at the apex. There were numerous petechiae over the lower part of the abdomen, the left arm, the neck and the chest. The right kidney was tender and palpable at the iliac crest. The spleen was just palpable. Culture of the blood revealed one hundred and fifteen colonies of *Str. viridans* per plate. The sulfadiazine level of the blood, determined on the day of her admission, was 113 mg per hundred cubic centimeters, and the urea nitrogen level was 150.4 mg. There was no oliguria. The sedimentation rate was 76 mm per hour by the Westergren method.

On November 11 continuous penicillin-heparin therapy was begun. The patient received approximately 200,000 Oxford units of penicillin each day, dissolved in 1,000 to 1,500 cc of isotonic solution of sodium chloride. Six

From the Department of Laboratories and the Department of Medicine, Jewish Hospital. Aided by grants from Friends of the Hospital and from the Dazian Foundation for Medical Research.

1 Weiss, S., and Rhodes, C. P. Healing and Healed Vegetative (Subacute Bacterial) Endocarditis, *New England J. Med.* **199**: 70, 1928.

2 Libman, E. A Consideration of the Prognosis in Subacute Bacterial Endocarditis, *Am. Heart J.* **1**: 25, 1922. A Further Report on Recovery and Recurrence in Subacute Bacterial Endocarditis, *Tr. A. Am. Physician* **48**: 44, 1933.

3 Hamman, L. Healed Bacterial Endocarditis, *Ann. Int. Med.* **11**: 175, 1937.

4 Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, *J. A. M. A.* **124**: 144 (Jan. 15) 1944. Loewe, L. The Louis Gross Memorial Lecture. The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis, *Canad. M. A. J.* **52**: 1 (Jan.) 1945.

also received approximately 200 mg of heparin (Liquaemin) daily, which was also incorporated in the isotonic solution. From a control level of twelve minutes, the coagulation time was maintained between thirty and sixty minutes throughout the course of therapy. Treatment was discontinued on November 25 after the patient had received a total of 2,740,000 Oxford units of penicillin and 2,500 mg of heparin. Cultures of the blood taken on November 19 and 29 and on December 6 showed no growth. During this course of therapy, the kidney and spleen gradually receded in size and finally became impalpable. Because the temperature did not return to normal, the patient was suspected of being in

date and remained so until her discharge on March 12. On March 7 the sedimentation rate was 25 mm per hour. Prior to her discharge it was noted that the character of the cardiac sounds had changed. At the apex there was a short rumbling presystolic and a long, high-pitched diastolic murmur. The high-pitched diastolic murmur was loudest at the fourth intercostal space just to the left of the sternum and could be faintly heard at the aortic area as well. While the blood pressure on her admission was 120 systolic and 80 diastolic, on discharge the tension was 126 systolic and 40 diastolic. She was discharged with a diagnosis of healed subacute bacterial endocarditis and aortic insufficiency.



Fig 1 (case 1)—Mitral valve ring showing increased vascularity compatible with old rheumatic infection. Hematoxylin and eosin,  $\times 75$ .

the clinically active but bacteria-free stage of the disease. Culture of the blood taken on December 8 revealed three colonies of *Str. viridans* per plate, and, accordingly, penicillin-heparin therapy was again started, on December 9. She was given intravenous therapy continuously for thirty-one days until Jan 8, 1944, receiving a total of 6,000,000 Oxford units of penicillin and 5,600 mg of heparin during this period. Two cultures of blood taken during the course of treatment were sterile, as were ten others made at approximately weekly intervals after the treatment up to March 7. On January 12, the patient menstruated for the first time since October. Her temperature became normal about this

date and remained so until her discharge on March 12. On March 7 the sedimentation rate was 25 mm per hour. Prior to her discharge it was noted that the character of the cardiac sounds had changed. At the apex there was a short rumbling presystolic and a long, high-pitched diastolic murmur. The high-pitched diastolic murmur was loudest at the fourth intercostal space just to the left of the sternum and could be faintly heard at the aortic area as well. While the blood pressure on her admission was 120 systolic and 80 diastolic, on discharge the tension was 126 systolic and 40 diastolic. She was discharged with a diagnosis of healed subacute bacterial endocarditis and aortic insufficiency.

**Subsequent Course**—Despite greatly restricted physical activity, administration of digitalis and limitation of her intake of fluids, the patient's compensation gradually decreased. The liver increased in size and tenderness, and she finally became dyspneic and orthopneic even with complete rest in bed.

**Final Hospitalization**—The patient had to be admitted to the New Rochelle Hospital on April 19 because of severe congestive heart failure. Physical examination revealed the heart to be grossly enlarged to the right and left. The liver was tender and palpable below the um-

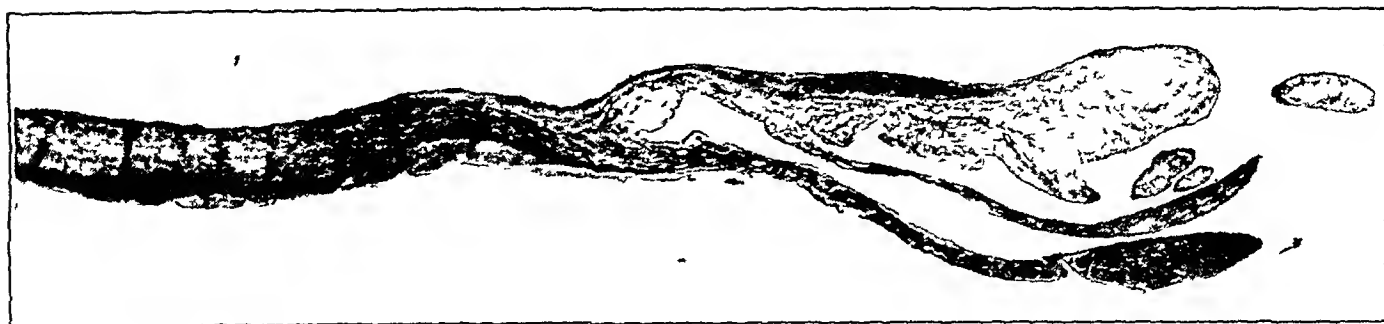


Fig 2 (case 1) —Mitral valve leaflet with endothelialized nodules composed of loose fibrous connective tissue. These may represent healed, organized vegetations. Hematoxylin and eosin,  $\times 11$

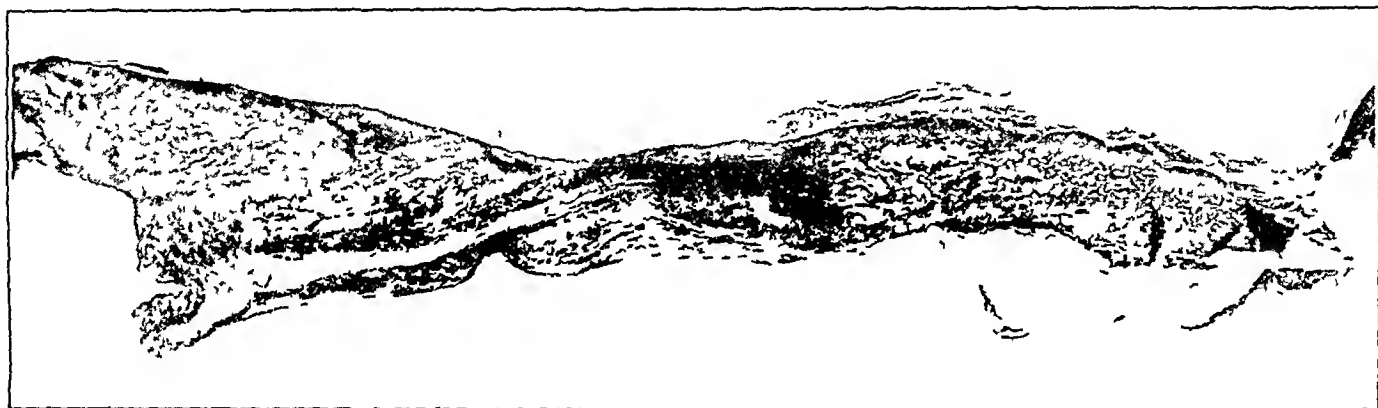


Fig 3 (case 1) —Anterior aortic cusp, low power view of thickened, fragmented valve. Hematoxylin and eosin,  $\times 11$

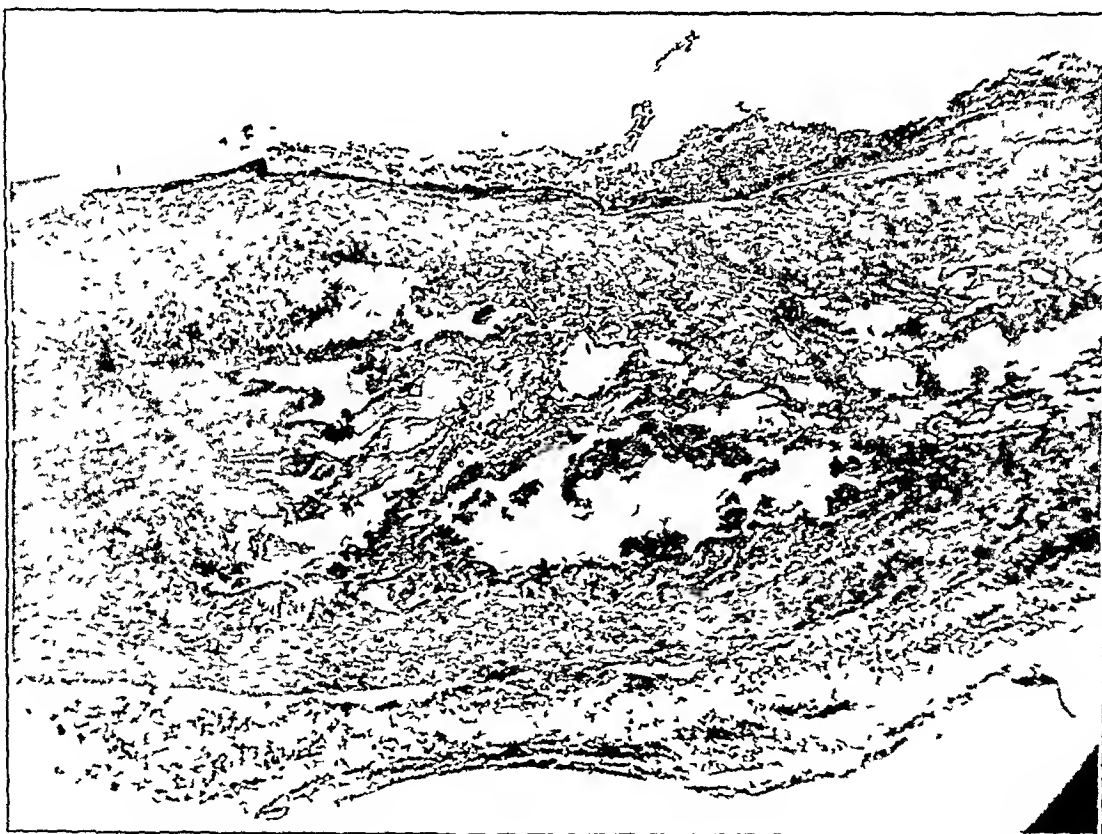


Fig 4 (case 1) —Higher magnification of figure 3 showing accretion of loose fibrinous meshwork to the endothelial surfaces of the distal portion of the valve and spongy, fragmented center of valve. Hematoxylin and eosin,  $\times 48$

bilicus The pulse rate was irregular, of Corrigan type and 106 per minute The blood pressure was 120 systolic and 0 diastolic

Despite therapy, the patient died on April 21 An electrocardiogram taken the day prior to death showed sinus tachycardia and right ventricular strain

*Observations at Autopsy* (by Dr J W Denton and Dr A F Heyl)—The body was that of a well developed, well nourished white woman The skin, conjunctivas and mucous membranes were pale There

**Cardiovascular System** The heart weighed 560 Gm The atria were extremely distended, especially the right The right ventricular wall measured up to 0.6 cm in thickness and the left 1.8 cm The myocardium was firm and red-brown The tricuspid and pulmonary valves were not remarkable The mitral valve was slightly thickened along the contact borders The aortic orifice admitted the index finger with ease The anterior and middle cusps were strikingly deformed The free portions appeared thickened, foreshortened, gray and

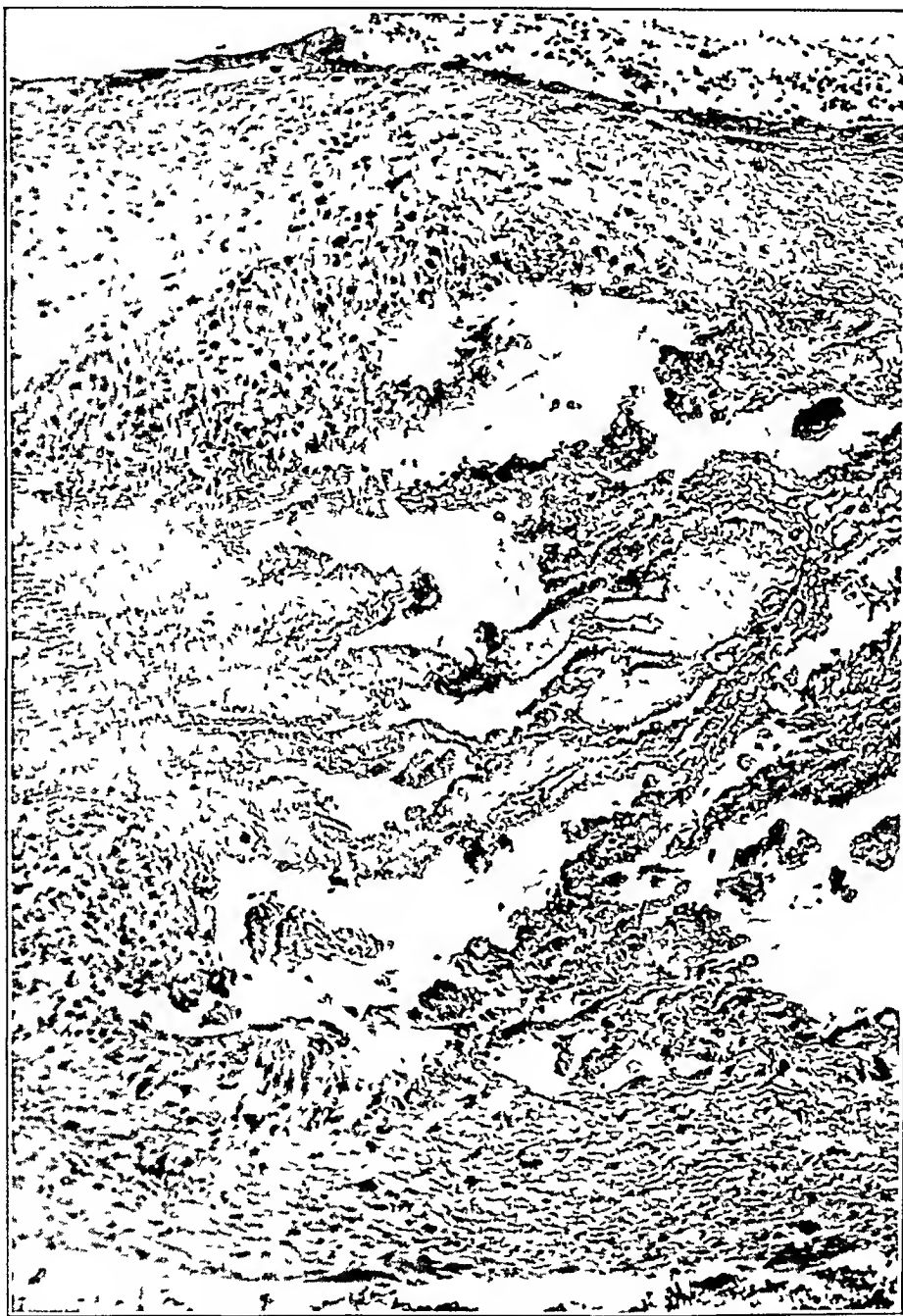


Fig 5 (case 1)—Higher magnification of figure 4 to show detail of central fragmentation of collagen Note palisading of fibroblastic cells at periphery No bacteria are seen Hematoxylin and eosin,  $\times 120$

were no petechiae The superficial lymph nodes were not palpable

**Body Cavities** The peritoneal cavity contained about 200 cc of clear yellow fluid and the pericardial cavity about 80 cc of a similar fluid The right and left pleural cavities contained, respectively, 400 and 150 cc of similar serous fluid The serous surfaces were all smooth and glistening

shredded, allowing portions of the valve to flap back and forth freely in the blood stream The shredded valve cusps were granular and appeared to be partially calcified in places Attached to them was a soft yellow and red blood clot The coronary ostia and arteries showed nothing of note The elasticity of the aorta was good

**Respiratory Tract** Both lungs were pink mottled with dark red externally. Crepitus was diminished, and the lungs cut with moderate resistance. There were, however, no definite areas of consolidation. The cut surfaces were grayish red and moderately wet. In the lower lobe of the left lung were two small, dark red wedge-shaped infarcts. The bronchi contained frothy fluid material. The pulmonary vessels were not remarkable.

**Gastrointestinal Tract** The esophagus, stomach and small, and large intestines showed nothing of note.

**Biliary System** The liver was moderately enlarged, purple-red and smooth. The mottling of passive congestion was readily visible through the capsule and was much more evident on section. The gallbladder and biliary ducts were not remarkable.

capsule was stripped with ease, revealing a congested, red-brown surface, which was slightly granular. In the cut surfaces, cortex and medulla were well demarcated and in the usual proportions. There were no petechiae. The left kidney weighed 210 Gm and was similar to the right. The renal pelves, ureters and urinary bladder showed nothing of note.

**Spleen** The spleen was firm and weighed 400 Gm. The external surface was purple-gray, and the capsule was tense. In the cut surfaces the follicles were large, numerous and distinct. The pulp was deep red and abundant.

**Genitalia** The uterus contained two small leiomyomas. The ovaries and fallopian tubes showed nothing of note.

**Cranial Cavity** The cranial cavity was not examined.



Fig 6 (case 1)—Middle aortic cusp with liquefaction necrosis in central portion of cusp and shredding at the periphery. Hematoxylin and eosin,  $\times 11$ .



Fig 7 (case 1)—Kidney, showing small wedge-shaped cortical scar. Hematoxylin and eosin,  $\times 50$ .

**Pancreas** The pancreas was normal in appearance.

**Adrenal Glands** The adrenal glands were of usual size and shape and showed nothing of note.

**Renal System** The right kidney weighed 190 Gm. The peripelvic adipose tissue was edematous. The

**Histologic Examination—Heart** In a preparation from the left side of the heart, including the mitral valve, the epicardium was found to be of usual thickness. The myocardium was broad and composed of slender fibers which stained well. Striations were moderately distinct. The interstitial tissue was only slightly increased in amount and density, and in places there were a few small perivascular spindle-shaped areas composed of dense fibrous tissue. At the valve ring (fig 1) the connective tissue was loose and harbored an increased number of small, well formed blood vessels. The valve itself showed nothing of note and did not appear thickened. Examination of the atrial wall revealed some thickening of the endocardium but otherwise nothing of note. Another preparation of the mitral valve (fig 2) showed a different picture. It was slightly thickened, and at the distal extremity and along its extent there were small subendothelial rounded nodular areas composed of loose fibrous tissue which was arranged in whorls. Section of the anterior cusp of the aortic valve (figs 3, 4 and 5) revealed a remarkable picture. The valve was thick and composed of dense hyalinized fibrous tissue in its proximal portion. As the free border was approached, the central portion of the valve appeared fragmented, and there were irregular patches of dense, pink-staining acellular collagenous tissue, which were interspersed with clear spaces. At the periphery was denser cellular fibrous tissue. There was some palisading of deeply staining fibroblastic cells toward the center of the valve. Attached to both endocardial surfaces of the valve was a loose fibrinous meshwork on which red and white blood cells were seen. The free edge of the valve was completely shredded, and the continuity of the endocardium had been lost. Sections stained by the Gram-Weigert method failed to reveal organisms.

either within the valve or on the surfaces. Preparations from the middle cusp of the aortic valve (fig 6) were similar. Here the core of the valve appeared cystlike and contained homogeneous pink-staining material. The free edge was likewise fragmented and disorganized. In one place there was a deposit of blue-staining calcific material.

**Lungs** Preparations from the two lungs were similar. The alveolar walls were somewhat thickened, and the air spaces were filled with large numbers of mononuclear cells containing golden brown pigment

spaces either were empty or contained small amounts of homogeneous or granular pink-staining material. Small amounts of precipitated protein were also seen within the lumens of the convoluted and collecting tubules. No lesions suggestive of focal embolic glomerulonephritis were seen. On the other hand, there were scattered glomeruli which appeared more cellular than usual. In these, the capillary tufts were inconspicuous, and the endothelial cells were large and hyperchromatic. Some of the tufts also contained numbers of polymorphonuclear leukocytes (fig 8).

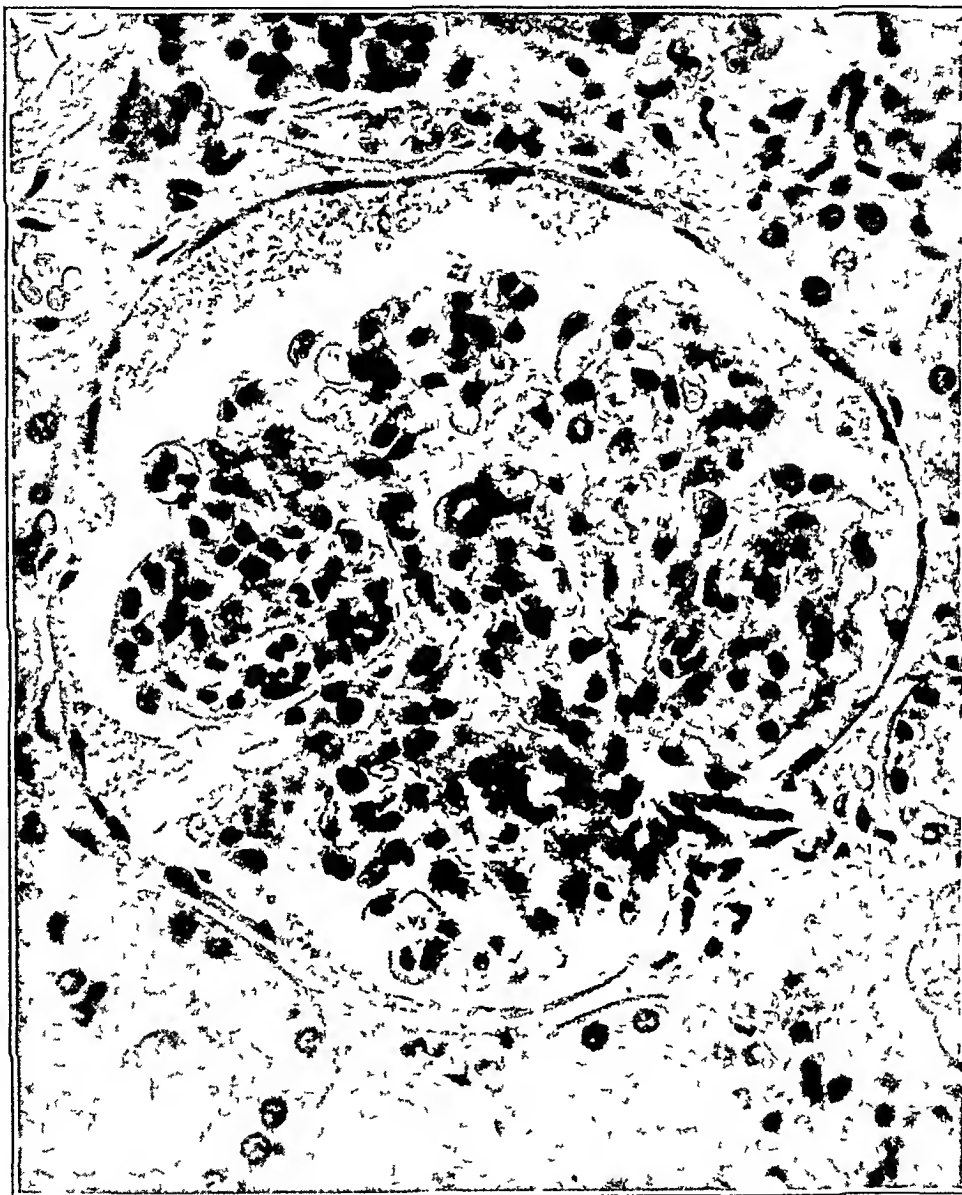


Fig 8 (case 1)—Glomerulus showing amorphous material within capsular space, note increased cellularity, cohesion of tufts and collections of polymorphonuclear leukocytes. Hematoxylin and eosin,  $\times 450$

granules. In places the alveoli contained homogeneous pink-staining material. The blood vessels were engorged.

**Liver** Sections of the liver revealed severe central necrosis with pronounced dilatation of the central veins and sinusoids.

**Kidneys** Sections taken from the two kidneys were similar. There were small scattered cortical wedge-shaped scars (fig 7) in which were hyalinized glomeruli, thickened small blood vessels and accumulations of small and large round cells. Otherwise the glomeruli were numerous, well formed and well distributed. The intraglomerular capillaries were distended, and the capsular

**Spleen** The follicles were large and increased in number, and there was striking hyperplasia of the germinal centers (fig 9). The pulp was cellular and hyperplastic, and the sinus walls were difficult to make out.

Postmortem aerobic and anaerobic cultures of the blood and of portions of the aortic valves showed no growth.

The anatomic diagnoses were fragmentation of the anterior and the middle cusps of the aortic valve, with insufficiency, healed mitral endocarditis, hypertrophy and dilatation of the heart, bilateral hydro-

thorax, ascites, passive congestion of the viscera, stasis infarcts in the left lung, scars in the kidneys, and acute intracapillary glomerulitis

#### SUMMARY OF CASE AND COMMENTS

This was a case of subacute bacterial endocarditis due to *Str. viridans* of at least seven months' duration prior to hospitalization. Therapy with massive doses of sulfonamide drugs failed to sterilize the blood stream. On the patient's admission the right kidney was tremendously enlarged, perhaps owing to infarction, the spleen was palpable, and cultures of the blood showed growth of organisms. She received two courses of combined penicillin-heparin therapy, with totals of 8,940,000 Oxford units of penicillin

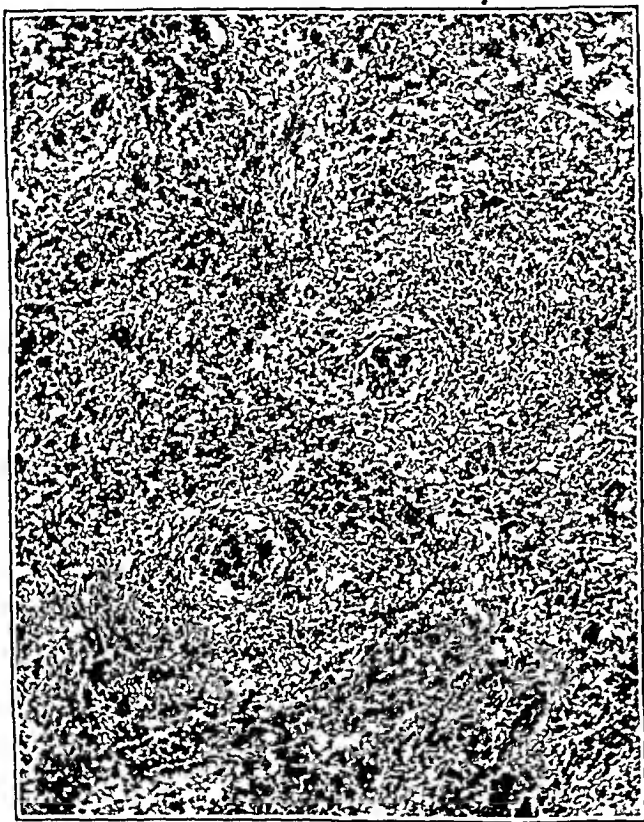


Fig 9 (case 1)—Spleen, showing follicular hyperplasia. Hematoxylin and eosin,  $\times 53$

and 7,100 mg of heparin given. She was discharged four months after her admission, bacteria-free and asymptomatic except for moderate cardiac embarrassment due to congestive phenomena. Despite vigorous therapy at home, congestive failure became more apparent, and she died fifteen weeks after treatment, or six weeks after hospitalization.

The demonstration at autopsy of a shredded aortic valve resulting in severe incompetency satisfactorily explained the intractable cardiac failure. That no bacteria could be demonstrated either histologically or by postmortem cultures was evidence confirming the conclusion that the

bacterial phase of the disease had been adequately dealt with. Obviously, however, the severe damage already done to the aortic valve was irremediable.

The conditions observed in the kidneys and spleen were of added interest. To begin with, the partial glomerular lesions so conspicuous in many patients with bacterial endocarditis were not present. However, there was evidence of a diffuse glomerulonephritis. This is of particular importance, because, according to Libman and Friedberg,<sup>5</sup> it is much more commonly found in the bacteria-free stage of the disease than in the active phase. Its development after the febrile disease has run its course speaks for a toxic (allergic) origin. The enlarged hyperplastic spleen probably has a similar origin. A remarkable feature of this case was the complete resolution of the massive right renal infarction, necropsy revealing but small cortical scars.

**CASE 2**—N. M. was a white woman, aged 29. She was admitted to the Jewish Hospital of Brooklyn on Feb 16, 1944, transferred from the Good Samaritan Hospital, Lexington, Ky. Her past history was noncontributory except for severe tonsillitis at the age of 2 or 3 years, after which cardiac murmurs were discovered. There was no history of scarlet or rheumatic fever. In November 1943, an infection of the upper respiratory tract developed, for which she was given sulfadiazine. In January 1944, she again suffered an attack of infection of the upper respiratory tract. A low grade persistent fever ensued, which failed to respond to acetylsalicylic acid or to sulfonamide compounds. Chills and fever appeared in February, and she was admitted to the Good Samaritan Hospital for diagnostic study. There it was found that cultures of the blood were positive for *Str. viridans*. On February 9 she had a sudden cerebral embolization, which rendered her completely aphasic. She was transferred to the Jewish Hospital of Brooklyn seven days later.

At the time of her admission, the patient was well developed and well nourished. She appeared pallid and chronically ill. Her speech was almost completely impaired. The temperature was 101 F, pulse rate 120 per minute, respiratory rate 30 per minute and blood pressure 160 mm of mercury systolic and 40 diastolic. There were several petechiae on the left hand. The heart was enlarged, and there were double mitral and aortic murmurs. The liver and spleen were both palpable 2 fingerbreadths below their respective costal borders. The reflexes were equal and active, and Babinski signs were not elicited. Culture revealed nine and eleven colonies of *Str. viridans* per cubic centimeter of blood. The sedimentation rate was 113 mm per hour (Westergren method), and there was moderate secondary anemia. The urine was normal. The clinical impression was subacute bacterial endocarditis implanted on a rheumatic background, with recent cerebral embolization.

Combined penicillin-heparin therapy by the intravenous route was begun the day after her admission to the hospital. She was given continuous therapy for twenty-three days, receiving 200,000 Oxford units of

5 Libman, E., and Friedberg, C. Subacute Bacterial Endocarditis, New York, Oxford University Press, 1941

penicillin per day and from 100 to 200 mg of heparin. The total dose was 4,600,000 Oxford units of penicillin and 2,900 mg of heparin. Her response to therapy was most gratifying. Cultures of blood, taken during therapy and afterward, showed no growth. Her speech cleared gradually, and on March 26 it was noted that there was only slight slurring. On April 13, the sedimentation rate was 16 mm per hour and the temperature curve was flat. The patient was discharged on April 17 for convalescent care at home.

*Subsequent Course* (by Dr T M Marks, Lexington, Ky) —On May 17, it was noted that the patient showed

diuretics. Repeated cultures of the blood were sterile. She died on August 7, approximately four months after having been discharged from the hospital, and twenty-two weeks after treatment.

*Observations at Autopsy* (by Dr E S Maxwell, Lexington, Ky) —The body was that of a well developed, moderately emaciated white woman. There was slight edema of the dependent portions. The peritoneum was smooth and glistening, and the cavity contained 800 cc of clear amber-colored fluid. Each pleural cavity contained about 400 cc of fluid.

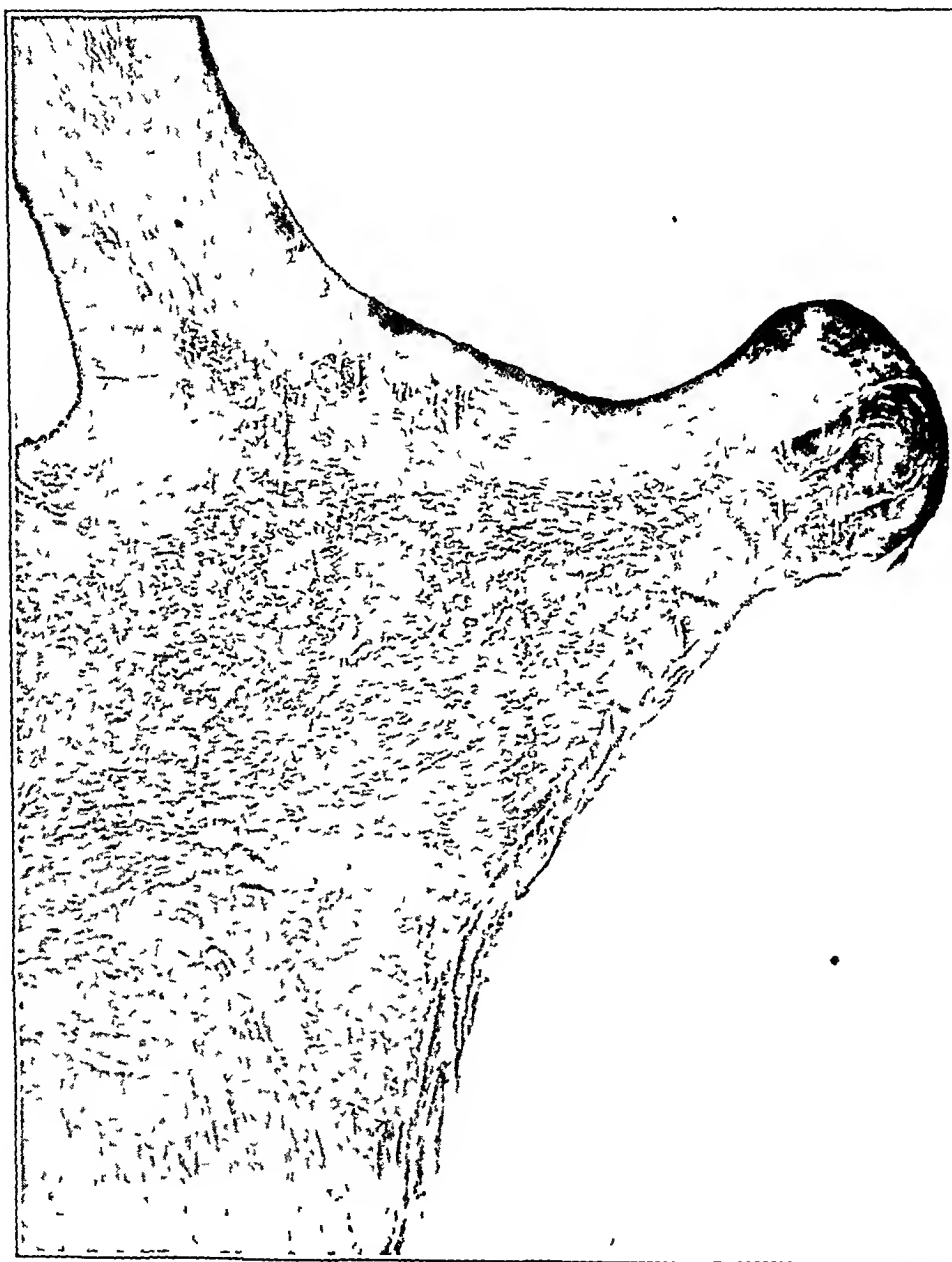


Fig 10 (case 2) —Aortic cusp, note fibrotic, stumplike character. Hematoxylin and eosin,  $\times 11$ .

remarkable improvement in her appearance. Her heart action was good, but she still had the murmurs from her primary heart disease. The blood pressure was 180 systolic and 70 diastolic. Culture of the blood showed no growth, the sedimentation rate was 8 mm per hour, and the blood count was normal.

From this time on, her cardiac status gradually deteriorated, and advanced congestive failure developed, which responded only slightly to digitalis and mercurial

The heart was large, weighing 600 Gm. The mitral leaflets were grossly normal, showing no ulceration, scarring or unusual thickening. The right aortic cusp was almost completely destroyed. The upper margins were short stubs and were brown and finely granular but completely free of vegetation. In the wall of the aorta, immediately above the attached margin of this cusp, there was an opening measuring 3 mm laterally and 5 mm perpendicularly. This opened into an

aneurysm-like sac measuring approximately 3 mm in diameter. This sac contained a small amount of fibrin, which was loosely attached. The wall of the aneurysm was of about the same thickness as the aorta and for the most part was smooth. The sac extended to the right, and the base of the right auricular appendage covered the roof of the aneurysm, while the wall of the



Fig 11 (case 2)—Aortic valve ring with definite fibrosis and collections of mononuclear cells harboring blood pigment. Hematoxylin and eosin,  $\times 98$

right auricle was adjacent to the aneurysm. The wall of the left ventricle was moderately hypertrophied. The apex was thin. The right side of the heart was grossly normal.

**Lungs** The right lung was moderately edematous. On the lateral surface of the upper lobe there was an infarct measuring 2.5 cm in diameter. The left lung showed moderate edema.

**Liver** The liver was approximately normal in size. The cut surfaces show definite nutmeg mottling.

**Kidneys** The kidneys were moderately enlarged and were dark purple-red in color. In the cut surfaces, the architecture was normal. The mucosa of the pelvis of each kidney was hemorrhagic. The ureters and urinary bladder were normal.

**Spleen** The spleen was moderately enlarged, weighing 250 Gm. Follicles were distinct.

**Histologic Examination**—**Heart** Sections from the short, thick aortic cusp (fig 10) revealed dense fibrosis with hyalinization but no inflammatory exudate. The surface was completely endothelialized. In the deeper layers, most prominently at the valve ring, there were collections of mononuclear cells harboring brown pigment granules (fig 11). Occasional lymphocytes and plasma cells were also seen. Sections of the myocardium showed small scattered areas of fibrosis. Preparations of the wall of the aneurysm revealed it to be identical in thickness and structure with the aorta. No inflammation was seen.

**Lungs** (fig 12) The alveolar walls were thickened, and in places there was ingrowth of spindle-shaped fibroblastic cells. The air spaces were filled with "heart failure cells." In some, there were numbers of polymorphonuclear leukocytes enmeshed in fibrin.

**Liver** There was extensive passive congestion with central necrosis. The central veins and sinusoids were distended.

**Pancreas** The acinar arrangement was orderly. Islands of Langerhans were numerous, well formed and well distributed. The interstitial connective tissue was slightly increased in amount.

**Adrenal Glands** The corticomedullary distinction was orderly. The cells of the cortical layer appeared swollen and fragmented in places, and some of the nuclei were pyknotic or absent. The cytoplasm was granular or finely vacuolated. Medullary tissue was loose and abundant.

**Kidneys** Sections of the two kidneys were similar. Glomeruli were numerous, well formed and well distributed. Bowman's capsule was slightly thickened in some. The capsular spaces were empty. The glomerular tufts were distended, and the lining cells were occasionally prominent. The epithelium lining the convoluted and collecting tubules was poorly preserved. The blood vessels were not remarkable.

**Spleen** The capsule of the spleen was of usual thickness. Follicles were numerous, well formed and well spaced. No germinal centers were seen. The pulp was loose, and the sinusoids were distended. The blood vessels showed nothing of note.

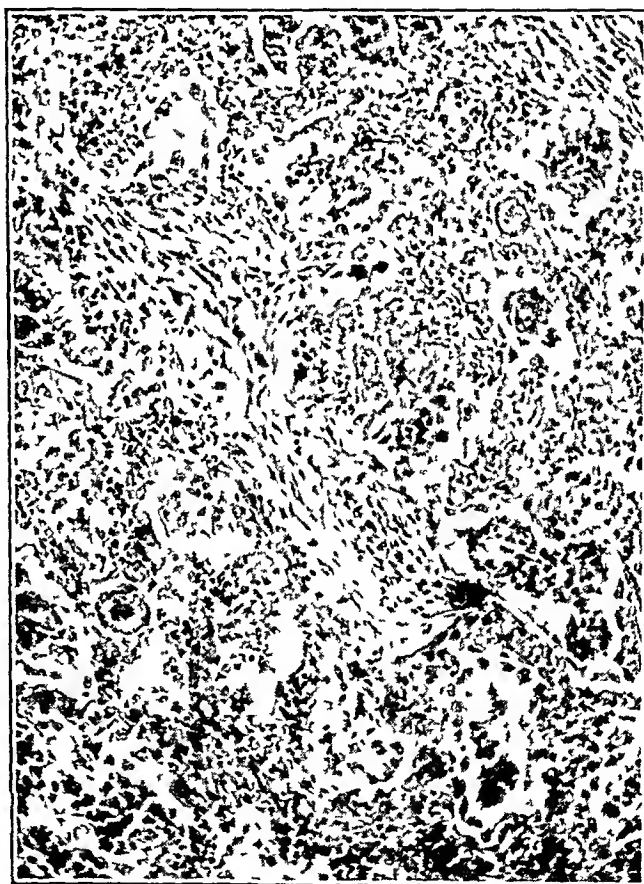


Fig 12 (case 2)—Lung, noticeable passive congestion with alveoli filled with "heart failure" cells. Note central area of fibrosis. Hematoxylin and eosin,  $\times 100$

The anatomic diagnoses were congenital aneurysm at the base of the aorta, healed aortic endocarditis, myofibrosis cordis, hypertrophy and dilatation of heart, bilateral hydrothorax, ascites, focal, terminal pneumonia, and passive congestion of the viscera.

## SUMMARY OF CASE AND COMMENTS

This was a case of subacute bacterial endocarditis of about one month's duration prior to the patient's hospitalization. An early manifestation of the disease was cerebral embolization, from which she recovered completely with therapy. The patient responded to treatment promptly, one course lasting twenty-three days being sufficient to effect permanent sterilization of the blood stream. The total dosage of penicillin was 4 600,000 Oxford units and of heparin 2,900 mg. Unfortunately, as in case 1, valvular damage was so extensive that compensation was not adequate for the long continuance of life. The stubby

aortic cusps found at necropsy allowed free reflux of blood into the left ventricle, and the severe valvular insufficiency resulted in progressive, intractable cardiac failure. The patient succumbed five and one-half months after treatment. An interesting feature was the presence of an aneurysm, probably congenital, at the base of the aorta.

## CONCLUSIONS

Two cases of healed subacute bacterial endocarditis were encountered. Death in both instances was due to cardiac failure incident to aortic valvular insufficiency.

## STUDIES ON HYPERTENSION

### IV BIOASSAY OF VASOCONSTRICTOR SUBSTANCES IN ULTRAFILTRATES OF CITRATED BLOOD PLASMA FROM PATIENTS WITH NORMAL BLOOD PRESSURES, PATIENTS WITH ESSENTIAL HYPERTENSION AND PATIENTS MADE HYPERTENSIVE BY INTRAVENOUS INJECTIONS OF ANGIOTONIN (HYPERTENSIN)

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Since the results of previous investigations<sup>1</sup> did not support the humoral origin of essential hypertension, it was concluded<sup>1c</sup> that "Final proof awaits conclusive demonstration of the presence or absence of angiotonin in increased amounts in the blood of patients with essential hypertension"

This report deals with a study of whether vasoconstrictor substances are present in increased amounts in the blood of patients with hypertension. The conclusion has been sought through a biologic assay of vasoconstrictor substances in the blood of patients with normal blood pressures, the blood of hypertensive patients and the blood of patients made transiently hypertensive by intravenous injections of angiotonin

#### LITERATURE

There are conflicting reports in the literature regarding the presence of pressor compounds in the blood of hypertensive patients or in the blood of animals made hypertensive by renal ischemia. Danzer, Brody and Miles<sup>2</sup> reported that the blood of patients with hypertension contained a pressor substance not found in the

blood of rabbits or in the blood of patients with normal blood pressures. Curtis, Moncrieff and Wright<sup>3</sup> repeated the work of Danzer and his associates but found no pressor substance in the blood of patients with hypertension. Both investigations may be criticized, because blood of human beings was injected into animals of another species; the cat. Bohn<sup>4</sup> claimed that he had demonstrated a pressor substance in an alcoholic, protein-free extract of citrated blood from pale hypertensive patients (nephritic) but that similar extracts of blood from both normal persons and plethoric hypertensive patients (with essential hypertension) produced a fall in blood pressure. He, too, injected extracts of human blood into animals of a heterologous species. De Wesselow and Griffiths<sup>5</sup> were unable to confirm Bohn's results. They could adduce no evidence of a pressor substance in the blood of patients with essential hypertension. Ultrafiltrates from plasma showed no effect, with the exception of a slight pressor effect produced by an ultrafiltrate of blood from a patient with chronic glomerulonephritis with slight renal failure. Aitken and Wilson<sup>6</sup> also were unable to confirm the claim of Bohn that blood of pale

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The Eli Lilly Company Laboratory of Clinical Research, I H Page, Director, furnished angiotonin for this study

1 (a) Gregory, R, Lindley, E L, and Levine H. Studies on Hypertension. I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients with Hypertension, *Tex Rep Biol & Med* **1** 59-76, 1943, (b) II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients. Its Possible Bearing on the Pathogenesis of Essential Hypertension, *ibid* **1** 167-206, 1943. (c) Gregory, R., Levine, H., and Lindley, E L. Studies on Hypertension. III. The Site of Action of Angiotonin, the Pressor Effects of Angiotonin on Patients Having Essential Hypertension, and Possible Relationships to the Pathogenesis of Essential Hypertension, *ibid* **2** 121-134, 1944

2 Danzer, C S, Brody, J G, and Miles, A L. On the Existence of a Pressor Substance in the Blood of Clinical Cases of Hypertension, *Proc Soc Exper Biol & Med* **23** 454-457, 1926

3 Curtis, F R, Moncrieff, A A, and Wright, S. The Supposed Presence of a Pressor Substance in the Blood of Patients with High Blood Pressure, *J Path & Bact* **30** 55-59, 1927

4 Bohn, H. Untersuchungen zum Mechanismus des blassen Hochdrucks. I. Gefassverengernde Stoffe im Blute beim blassen Hochdruck, *Ztschr f klin Med* **119** 100-139, 1932

5 de Wesselow, O L V S, and Griffiths, W J. On the Question of Pressor Bodies in the Blood of Hypertensive Subjects, *Brit J Exper Path* **15** 45-52, 1934

6 Aitken, R S, and Wilson, C. An Attempt to Demonstrate a Pressor Substance in the Blood in Malignant Hypertension, *Quart J Med.* **28** 179-190, 1935

hypertensive patients contained a pressor substance. Page<sup>7</sup> reported that ascitic fluids, as well as blood and cerebrospinal fluids of normal persons, contained a pressor substance. He could not demonstrate any increase of this pressor substance in the blood or cerebrospinal fluid of patients having hypertension. Interestingly, he observed that the medulla and spinal cord were essentially instrumental in the production of this pressor effect. Fasciolo, Houssay and Taquini<sup>8</sup> stated that blood from the renal vein of an ischemic kidney of a dog contained more pressor substance than blood which had passed through a normal kidney of a dog. They used a perfusion technique on the South American toad. Using frogs, bullfrogs and toads from the southern part of the United States of America, Mason and Rozzell<sup>9</sup> were unable to confirm the results of Houssay and co-workers. The use of such widely different species as the dog and the frog is again open to criticism. Page,<sup>10</sup> using a perfused rabbit's ear, concluded that "since vasoconstriction occurs under the same experimental conditions with plasma from both hypertensive patients and dogs, this is considered cogent evidence in favor of the view that the chemical mediator of both is similar and is possibly angiotonin."

While the methods used are perhaps open to question on the grounds mentioned, the results of injecting blood, plasma or extracts of blood and of plasma from hypertensive patients into other animals have failed to demonstrate conclusively the presence of an excessive amount of pressor substance in the blood of hypertensive patients.

#### METHOD OF STUDY

At the beginning of these studies, citrated plasma from normal persons and from hypertensive patients was injected into small dogs (3 to 4 Kg.) arranged for the kymographic recording of the blood pressure. This procedure was immediately abandoned because of the extreme depressor effects on dogs of plasma from both normal and hypertensive patients.

Ultrafiltrates of citrated plasma were next injected into small dogs. In general, only a suggestive or doubtful increase of blood pressure was produced by the ultrafiltrate from blood to which a known pressor amount of

angiotonin had been added, compared to an ultrafiltrate of the same blood without the added angiotonin. The dogs were then abandoned as being unsuitable experimental animals for this purpose.

In all the subsequent experiments we have used Wisconsin winter frogs. They were kept in an ice box at about 4°C and allowed to be at room temperature from two to four hours before they were to be used. Bioassays were made on them after complete pithing was performed. Perfusion of the entire frog was done at a constant perfusing pressure of 15 cm. with a cannula placed in the truncus arteriosus. The sinus venosus was slit to permit egress of the perfusing fluid, and the webs of the hindfeet were slit to retard the development of edema. The animal thus prepared was perfused on an inclined board, and the number of drops in each two minute interval was recorded with an automatic drop recorder. The volume of perfused fluid collected in a two minute interval was also measured. In general, five intervals of two minutes each were employed for both control and experimental periods, although the perfusion was often extended beyond five two minute intervals.

In nearly all instances the frog was perfused with calcium-free frog Ringer solution<sup>11</sup> to wash out the vascular system as well as for a control against which the experimental solutions were tested. The calcium-free frog Ringer solution contained 0.4 per cent sodium citrate, the same amount as that contained in the blood plasmas from which our ultrafiltrates were made. In some instances, indicated in the proper table, dibasic sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) was added to bring the pH to about 8.3.

Care was observed to see to it that temperatures of all solutions perfused through any one frog were the same. Perfusions were done at room temperature and ranged from 25°C to 30°C.

The effect of changes in hydrogen ion concentration on the perfusion rate was studied, and it was found that there was no effect within the limits of 7.3 to 8.4, the range over which our studies were made.

An attempt was made to perfuse these frogs with human plasma according to the method employed by Houssay and Taquini<sup>12</sup> with dog's plasma. We found that even when the calcium-free citrated frog Ringer solution was employed for a 1:8 dilution of the plasma, the vasoconstrictor action was too intense to permit us to use this method. We therefore decided that such dilutions interfered with usefulness and decided to use ultrafiltrates solely.

In all the experiments subsequently reported in this paper we have used the following ultrafiltrates to bioassay the vasoconstrictor substances by the method described:

- 1 Ultrafiltrates of citrated plasma from 5 persons with normal blood pressures
- 2 Ultrafiltrates of citrated plasma from 9 patients with hypertension
- 3 Ultrafiltrates of citrated plasma from 8 patients whose blood pressures had been raised by intravenous injections of angiotonin

11 The composition of frog Ringer solution is as follows:

	Regular %	Alkaline %
Sodium chloride	0.65	0.45
Potassium chloride	0.014	0.014
Calcium chloride	0.012	0.012
Sodium bicarbonate	0.020	0.20

This solution was modified for the purposes of these experiments as described in the text.

12 Houssay, B. A., and Taquini, A. C. Accion vasoconstrictora de la sangre venosa del riñon Isquemado, *Rev Soc argent de biol* 14: 5-14, 1938.

7 Page, I. H. Pressor Substances from the Body Fluids of Man in Health and Disease, *J. Exper. Med.* 61: 67-96, 1935.

8 Fasciolo, J. C., Houssay, B. A., and Taquini, A. C. The Blood-Pressure, Raising Secretion of the Ischaemic Kidney, *J. Physiol.* 94: 281-293, 1938.

9 Mason, M. F., and Rozzell, J. D. Attempts to Demonstrate Vasopressor Properties in the Serum of Hypertensive Dogs, *Proc. Soc. Exper. Biol. & Med.* 42: 142-144, 1939.

10 Page, I. H. The Vasoconstrictor Action of Plasma from Hypertensive Patients and Dogs, *J. Exper. Med.* 72: 301-310, 1940.

Blood was obtained rapidly (in one to two minutes) in all cases by puncture of the femoral artery. It was drawn into a sterile evacuated bottle containing 10 cc of 4 per cent solution of sodium citrate per hundred cubic centimeters of withdrawn blood. In general, 200 cc of blood was withdrawn from each patient into each of two different bottles at an interval of five to ten minutes. The two bleedings were done in order to maintain similar conditions for all subjects, since when we injected angiotonin intravenously we first withdrew 200 cc as a control and later withdrew an additional 200 cc of blood when the systolic blood pressure was at its peak of about 180 to 200 mm of mercury. Patients with normal and elevated pressures were bled similarly in two different 200 cc amounts in order to have the procedures identical in all groups.

Blood was taken from the femoral artery for two reasons primarily, because it was believed that the concentration of angiotonin might be higher in arterial blood than it would be in venous blood after the blood had circulated through the peripheral tissues, and, secondly, so that a 200 cc sample could be obtained quickly during the peak of the blood pressure elevations resulting from the intravenous injection of angiotonin.

Immediately after the blood was withdrawn, it was placed in cracked ice with a minimum of agitation to prevent hemolysis. As rapidly as possible, the blood was centrifuged in sterile 50 cc tubes. The citrated plasma was transferred to the ultrafiltration apparatus with precautions for asepsis. No plasma prepared in this fashion showed hemolysis. We have employed an ultrafiltration apparatus previously described by one of us.<sup>13</sup>

Ultrafiltration was carried out in bags made from cellophane "osmosis membrane" and of such length and diameter as to take 100 to 125 cc of citrated plasma. All ultrafiltrations were done in a mechanical refrigerator with the temperature at about 4 C.

## RESULTS

**Control Studies**—It was established by trial that 5 to 10 cc of the available angiotonin solution would raise the systolic blood pressure of an average adult to levels of 180 to 200 mm of mercury. It was felt that this amount represented a dilution of 1:500 to 1:1,000 of the injected solution of angiotonin. Accordingly, it was considered necessary to establish whether our method of bioassay would detect dilutions of this order. The results in table 1 indicate in general the ranges of effective strengths. Dilutions of 1:10,000 angiotonin in calcium-free citrated frog Ringer solution were not effective, of 1:1,000 were usually effective, and of 1:500 were always strikingly effective. It may be noted further that the vasoconstrictor effects of angiotonin were always manifested by the second two minute perfusion interval and that there was always a recovery to or toward the preultrafiltrate levels when ultrafiltrates were followed by calcium-free citrated frog Ringer solution.

Analysis of the data in table 1 will show that frequent assays of a known dilution of the angiot-

onin were done over the period during which our experiments were in progress. They were done to make sure our angiotonin did not deteriorate in strength. We had no reason to believe it would, because our stock was kept at 4 C and all withdrawals were made with strict precautions for asepsis. They were done to make sure also that the various lots of frogs remained responsive to angiotonin.

TABLE 1—Effects on the Perfusion Rate of 1:1,000 and 1:500 Angiotonin in Calcium-Free Citrated Frog Ringer Solution

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals			
Frog	No 1	No 2	No 3
Date	4/15/44	5/17/44	5/19/44
Control with frog Ringer solution	72	105	63
	70	110	64
	72	113	64
	72	117	64
	70	124	65
	127		
1 1,000 angiotonin	32	110	62
	30	87	52
	23	78	56
	22		48
	20		50
Return to frog Ringer solution	30	84	58
	30	103	52†
	30	102	55
	32	100	57
	34	108	57
	110	58	

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals					
Frog	No 4	No 5	No 6	No 7	No 8
Date	5/19/44	5/20/44	5/19/44	6/15/44	6/15/44
Control with frog Ringer solution	93	119	122	94	80
	93	119	125	88	74
	93	64*	119	87	78
	93	98	111	92	78
	95	84	111	94	78
			106	94	78
				94	
1 500 angiotonin	85	64	112	92	74
	55	49	94	73	62
	49	43	80	60	53
	47	43	70	58	49
	47	43	64	57	47
Return to frog Ringer solution	53	45	62	52	47
	63	56	78	61	52
	67	55	92	69	56
	68	54	98	72	57
	70	58	95	74	57
			75	58	56

\* Ran out of perfusion fluid

† Pressure down

Detailed consideration of the figures will show that whereas there is evidence that 1:1,000 dilution of our angiotonin solution frequently produced vasoconstriction, 1:500 dilutions never failed to produce vasoconstriction, as shown by a decrease in the volume of perfusate during the ten or more minutes of the test. It may also be seen that the volume of perfusate in a two minute period invariably increased after the return to calcium-free citrated frog Ringer solution from the known angiotonin solution. It usually did not return to the volume of perfusate

13 Gregory, R., and Andersch, M. The Filterable Calcium of Blood Serum, *Am J M Sc* **191** 263-271, 1936

obtained before the angiotonin perfusion was started. But there was always a definite increase, a result contrary to that which would be obtained if the decrease during the period of perfusion with angiotonin was a manifestation of the frequently observed tendency of the per-

TABLE 2 A—*The Vasoconstrictor Effects of (a) 1 500 Solution of Angiotonin in Calcium-Free Citrated Frog Ringer Solution, (b) Ultrafiltrate of a 1 500 Solution of Angiotonin in the Same Frog Ringer Solution and (c) Solution Remaining in the Sac After Twelve Hours of Ultrafiltration of a 1 500 Angiotonin Solution in the Same Frog Ringer Solution*

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals		
Frog Date	No 1 8/1/44	No 2 8/1/44
Alkaline frog Ringer solution with 0.4% sodium citrate + 2 cc fifth molar solution of dibasic sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) per liter at $\text{pH}$ 8.5, $T$ 38° C	52 64 60 70 73 74	10.5 10.4 10.4 10.1 10.0
1 500 angiotonin in frog Ringer solution as above $\text{pH}$ 8.5	72 58 51 50	8.4 6.2 5.6
Control frog Ringer solution $\text{pH}$ 8.5	64 70 76 76 77	5.1 6.8 7.8 7.8 7.8 7.7

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals								
Frog Date, 1944	No 3 8/2	No 4 8/2	No 5 8/2	No 6 8/2	No 7 8/4	No 8 8/4	No 9 8/4	No 10 8/4
Same frog Ringer solution as above	13.2 12.6 12.6 12.2 11.8 11.3	10.0 8.7 7.6 7.4 7.4 7.0			7.2 7.2 7.0 7.0 6.8 6.8		10.5 9.8* 8.1 8.2 8.0	
Ultrafiltrate of 1 500 angiotonin in frog Ringer solution *	11.2 11.0 9.8 9.4	6.6 5.4 5.6 5.8			5.8 5.0 4.0		8.0 7.0 6.4	
Control frog Ringer solution	9.4 9.6 9.2 8.2 7.8 7.3 7.4 7.2	7.0 7.3 7.3 7.4	10.8 10.6 10.1 9.2 8.6	6.3 5.8 5.5 6.3 6.1 6.4	4.6 5.0 5.0 5.1 5.2 5.2	15.6 14.0 12.5 12.8 13.4 13.4	6.6 7.1 7.4 7.0 7.3	6.2 6.2 7.5 5.0 7.8
Sac residue from ultrafiltrate of 1 500 angiotonin above	7.0 6.0 4.6 4.0	7.3 6.2 4.8	6.0 4.0 3.4	6.2 4.8 4.0 3.6		12.5 9.8 8.8		8.0 7.6 7.2 7.2
Control frog Ringer solution	4.0 3.8 4.0 3.8 3.7	4.8 5.2 5.4 5.6 5.2	3.6 3.6 3.6 3.6 3.3	3.8 4.3 4.4 4.4 4.3		8.8 9.6 10.2 10.1 9.8		6.6 6.8 7.0 7.2

\* Retried cannula

fusate volume to decrease gradually with time when calcium-free citrated frog Ringer solution alone is employed

From the data presented in table 1 it is concluded that (1) our frogs were sensitive to the vasoconstrictor action of the available angiotonin in dilutions of as much as 1 1,000 and always

in dilutions of 1 500 of the original stock of calcium-free citrated frog Ringer solution and (2) that our solutions of angiotonin remained potent during the period of our experiments

After it had been established that the frogs were sensitive to dilutions of 1 1,000 to 1 500 of angiotonin and inasmuch as our earlier experiments made us decide to use ultrafiltrates of citrated plasma, we next found it necessary to prove that angiotonin was ultrafiltrable. Consequently a known amount of angiotonin was added to calcium-free citrated frog Ringer solution and to human blood. These solutions were then treated as indicated in our discussion of methods. Four hundred cubic centimeters of blood was drawn as usual and citrated to usual

TABLE 2 B—*Vasoconstrictive Effects of an Ultrafiltrate of Blood Plasma and an Ultrafiltrate of Plasma of the Same Blood to Which Angiotonin Had Been Added in Proportion of One Cubic Centimeter to One Hundred Cubic Centimeters Blood*

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals		
	Frog No 1	Frog No 2
Control with calcium free citrated frog Ringer solution	5.3 5.4 5.5 5.7 5.9 6.1 6.3	15.8 14.2 15.4 15.2 15.0
Ultrafiltrate of plasma from plain blood	6.1 6.2 6.0 5.8 5.3 5.0	12.0 6.4 5.2 5.0 4.6 4.8
Ultrafiltrate from blood to which 2 cc angiotonin/200 cc blood had been added		
Return to frog Ringer solution	4.9 5.0 4.7 5.2 5.0 5.0 5.0 5.0	6.4 10.4 12.4 13.2 13.1 14.5

strength. This was divided into two portions. The first 200 cc was chilled, centrifuged and ultrafiltered as described. To the second 200 cc we added 2 cc of angiotonin and prepared an ultrafiltrate. Ultrafiltrates from these two different 200 cc portions were perfused through frogs. The results when angiotonin was added to calcium-free citrated frog Ringer solution are shown in table 2 A. The results when angiotonin was added to blood are shown in table 2 B.

Analysis of data in table 2 A according to our interpretation, shows that angiotonin is ultrafiltrable in calcium-free citrated frog Ringer solution. And while we do not believe we have done experiments numerous enough to be statistically significant, the data suggest that angiotonin does not filter quite as rapidly as water. This suggestion is based on the finding that

the solution remaining in the sac is slightly more vasoconstrictive than either the original solution or an ultrafiltrate

We have concluded from the data given in table 2 A and table 2 B that angiotonin is ultrafiltrable by our method, can be recovered in the ultrafiltrate from blood to which it has been added and can be detected in the ultrafiltrates from blood plasma by our method of bioassay

The relative usefulness of our method of ultrafiltration of citrated blood plasma compared to the use of 1/8 dilutions of plasma as employed by Houssay and Taquini to demonstrate vasoconstrictor substances in the blood from the renal veins of dogs prepared according to Goldblatt's method can be seen in table 3

These results show that the diluted blood plasma to which angiotonin had been added is no more effective than the same diluted plasma without angiotonin. Comparison of these results with those in table 2 B will undoubtedly allow one to conclude that the vasoconstrictor substances in citrated human plasma are in such strength that it is almost useless to try to remove them by dilution. It is obvious that an ultra-

TABLE 3—Effect of One to Eight Dilutions of Citrated Blood Plasma and Citrated Blood Plasma Containing Angiotonin on the Perfusion Rate

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals	
	Frog No 1
Control with calcium free citrated frog Ringer solution	80 84 82 68 53 78 76
1/8 dilution of patient's plasma	72 74 68 55 40 26
	Frog No 2
Control with the same frog Ringer solution	76 80 75 76 76 78
1/8 dilution of same patient's plasma from blood to which 1 cc angiotonin/100 cc blood had been added	63 60 56 42 28 18

filtrate from whole plasma contains much less vasoconstrictor substance than a 1/8 dilution of plasma. An ultrafiltrate has the further advantage in studies such as ours that the substance in the bioassay of which we are interested is not significantly diluted, but is presumably present in the ultrafiltrate in about the same strength as it is in the whole plasma

#### EFFECT OF CHANGES IN HYDROGEN ION CONCENTRATION ON PERFUSION RATE

Early in our experiments it was decided that it was necessary to take into account the possible effect of changes in hydrogen ion concentration on perfusion rate. It was then found that the calcium-free frog Ringer solution that we made

TABLE 4—Effect of Slight Changes in the  $p_H$  on the Perfusion Rate

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals	
Fresh Calcium Free Citrated Frog Ringer Solution, $p_H$ 7.35	Frog Ringer Solution That Had Been Made Up Several Days, $p_H$ 8.3
5.0	7.2
4.8	7.0
6.4	7.2
6.0	7.2
6.0	7.0
(Same frog perfused with solutions of different $p_H$ )	

with added 0.4 per cent sodium citrate varied in  $p_H$  from 7.3 to 7.6 approximately. Most of our plasma ultrafiltrates were found to range from  $p_H$  8.3 to  $p_H$  8.4. In most instances, the  $p_H$  of ultrafiltrates from the two different 200 cc samples of blood drawn from the same subject were practically identical. Because of this small difference, the effect of slight changes in  $p_H$  on perfusion rate was studied. The results are indicated in table 4. They are representative of many additional experiments which showed that changes in  $p_H$  from 7.3 to 8.3 had no effect or might, as we have just stated, slightly increase the rate of perfusion.

In view of these minor variations and of the additional fact that almost all of our ultrafiltrates from normal, angiotonin-treated and hypertensive patients had a  $p_H$  of about 8.3, it was thought that this similarity in concentration in itself was sufficient control. However, most of our work was done with calcium-free frog Ringer solution which contained 0.4 per cent sodium citrate (the same amount as that in citrated plasma) and 2 cc of fifth-molar solution of dibasic sodium phosphate ( $Na_2HPO_4$ ) per liter and having a  $p_H$  of about 8.3.

To summarize, we have concluded that any change in hydrogen ion concentration from calcium-free citrated frog Ringer solution to ultrafiltrates did not account for any of the observed changes. But to avoid any possible criticism most of our perfusion work was done using as perfusion control a phosphate-buffered calcium-free frog Ringer solution containing 0.4 per cent sodium citrate and having  $p_H$  8.3 almost uniformly.

# EFFECT OF SODIUM CITRATE IN CALCIUM-FREE FROG RINGER SOLUTION ON PERFUSION RATE

Because the citrated plasma employed contained 0.4 per cent sodium citrate, it was necessary to add that much sodium citrate to our calcium-free frog Ringer solution. In view of the identity of strength in both solution and plasma, it might not have been necessary to control this. Because of the effect of sodium citrate on ionized calcium, however, we did test the effect of a calcium-free frog Ringer solution as well as the addition of sodium citrate to a calcium-free frog Ringer solution on the perfusion rate. Table 5 contains some of the experimental data bearing on these points.

Examination of the data in table 5 shows that the results obtained by perfusing frogs with cal-

TABLE 5—The Effects of Four Tenths Per Cent Sodium Citrate on the Perfusion Rate

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals					
Frog	No 1	No 2	No 3	No 4	No 5
Regular frog	70	47	59	80	117
Ringer solution pH 7.35	74	54	52	84	158
	78	46	52	82	164
	76	60	49	80	158
Spilled		55	40	78	142
	85			76	154
	86				152
	98				150
Spilled					
	106				
	127				
	122				
	127				
	125				
	112				
	110				
Frog	No 6	No 7	No 8	No 9	
Calcium free	64	62	116	76	
frog Ringer	60	77	119	80	
solution +	58	79	122	75	
0.4% sodium	60	78	125	76	
citrate	58	78	119	76	
	59	81	120	78	
	58		116		
	59				
	57				
	58				
	56				
	54				
	52				
	54				
	55				
	54				
	53				
	53				
	52				
	53				
	47				
	49				
	48				
	47				

cium-free frog Ringer solution containing 0.4 per cent sodium citrate were not significantly different from those obtained with regular frog Ringer solution. The volume of perfusate was within the same range, the volume in each two minute interval tended to stabilize for about the same number of minutes and to show a tendency to gradual decline in volume with the passage of time.

Finally, it was considered necessary to study as a control the perfusion behavior when frogs were perfused for forty-five to sixty minutes with calcium-free citrated frog Ringer solution. Table 6 shows the data obtained in this study. It can be seen from this table that the volume of the two minute perfusates is constant at

TABLE 6—The Effect of Time on the Perfusion Rate with Calcium-Free Frog Ringer Solution Containing Four Tenths Per Cent Sodium Citrate and Two Cubic Centimeters Fifth-Molar Dibasic Sodium Phosphate ( $\text{Na}_2\text{HPO}_4$ ) Per Liter pH Ranging From 7.7 to 8.3

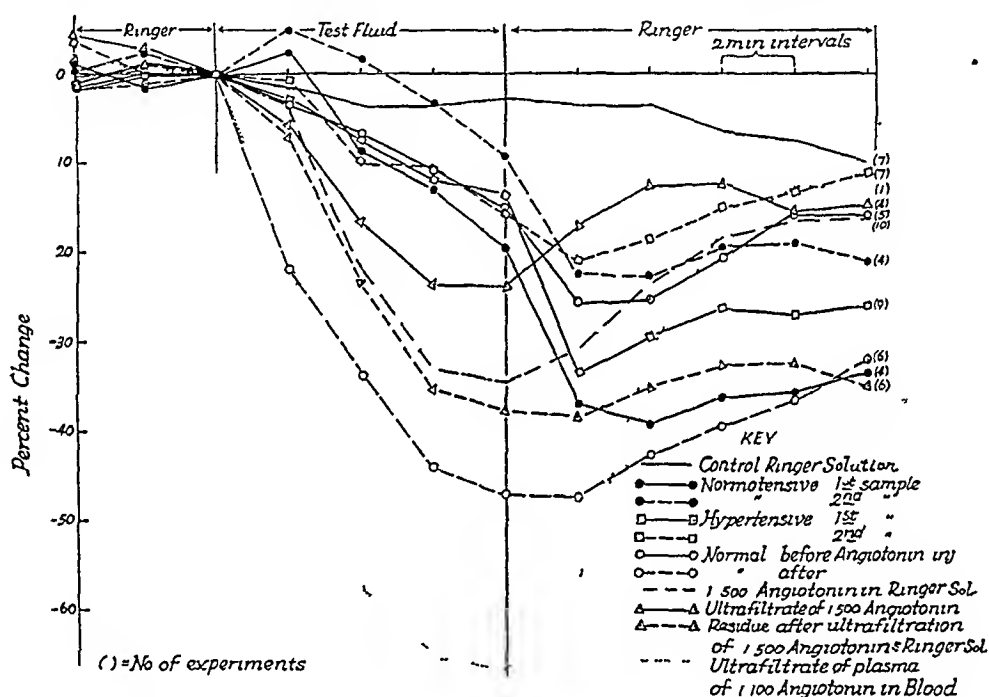
Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals						
Frog Date	No 1 6/13/44	No 2 6/6/44	No 3 6/13/44	No 4 5/26/44	No 5 5/26/44	No 6 5/11/44
	94	104	84	69	66	164
	100	96	86	78	70	165
	08	101	86	86	74	164
	101	108	91	84	74	175
	100	96	90	84	68	184
	101	96	88	79	69	168
	104	101	86	75	67	156
	104	101	82	78	62	174
	110	100	82	80	65	179
	110	90	78	79	64	182
	112	96	76	79	68	178
	112	92	66	79	69	174
	111	89	62	78	69	174
	107	84	72	78	68	170
	107	86	Lost	78	62	173
	108	85	59	73	66	157
	109	86	54	65	68	149
	108	81	55	58	66	152
	107	83	54	56	68	139
	102	77	52	51	67	132
	103	77	52	55	68	115
	102	76	50	49	68	102
	99		Considerable edema	48	67	100
	99			44	66	94
	93			40	62	80
					60	80
					58	82
					54	82
					53	83
					51	78
					50	64
					50	54
					51	48
					48	46
					48	46
					44	46
					43	
					40	

least for the first twenty minutes. In some frogs it is constant for periods considerably longer than twenty minutes. In other frogs there is a very gradual decline after the first ten periods. It may be concluded that the perfusion method is constant enough in the first twenty minutes or more to make apparent the effects of any vasoconstrictor substances present in plasma ultrafiltrates, which were always perfused through the frog within the time limits in which the data showed the perfusate volumes to be reasonably uniform.

From our control studies we have concluded (1) that perfusion of frogs by the method described results in uniform rates of perfusion, (2) that changes in hydrogen ion concentration from 7.3 to 8.3, the range of difference between some of our control frog Ringer solutions and

our plasma ultrafiltrates, apparently has no effect on the perfusion rate, (3) that calcium-free frog Ringer solution containing 0.4 per cent sodium citrate apparently has no inherently vasoconstrictor effect, (4) that whole or 1:8 dilutions of human plasma are entirely unsuitable for perfusion through the frog for our purposes because of the considerable amount of vasoconstrictor substance in citrated human plasma, (5) that frogs prepared for bioassay as we have described are often sensitive to dilutions of 1:1,000 and always sensitive to dilutions of 1:500 of the available angiotonin solution, (6) that the amount of angiotonin present in the blood when we have injected it and the amount found necessary to raise the patients' blood pressures to 180 to 200 mm of mercury systolic was about 1:500 dilution in whole blood or 1:250 in plasma

of drawing the second 200 cc portion. We were primarily concerned with this second 200 cc portion in our patients in whom angiotonin had been injected, because the first 200 cc was used as a control. Drawing so much blood might in itself theoretically cause the body to produce vasoconstrictor substances, accordingly we used this method of withdrawing two different 200 cc portions of blood from all of our three different types of patients. The work of Sapirstein, Ogden and Southard<sup>14</sup> and that of Collins and Hamilton<sup>15</sup> should be cited in this connection. These workers have demonstrated that large hemorrhages in experimental animals result in an increase of angiotonin. On the other hand, Page<sup>16</sup> reported that nephrectomy did not prevent the appearance of vasoconstrictor substances in the plasma of dogs that had been bled. On



Percentage change in volume of perfusion (in relation to flow immediately before test fluid)

and (7) that angiotonin added to human blood is ultrafiltrable and may be detected in plasma ultrafiltrates by the bioassay method used.

#### EXPERIMENTAL STUDIES

As a result of the aforementioned control studies, we have proceeded with experimental observations of bioassay of vasoconstrictor substances in ultrafiltrates of citrated plasmas from patients of three types: those with (1) normal blood pressure, (2) hypertension and (3) hypertension produced by intravenous injections of angiotonin.

From all patients the blood was drawn in two different 200 cc amounts, one immediately after the other. Ultrafiltrates of the plasma from both 200 cc portions were made and perfused in order to have a control of the effect

the basis of these results, Page has suggested that at least two substances are involved in hemorrhagic shock—a pressor substance from the kidney and a vasoconstrictor substance from elsewhere in the body.

#### I Effect of Ultrafiltrates of Plasma from Patients with Normal Blood Pressures—Ultrafiltrates of plasma from patients with normal

14 Sapirstein, L. A., Ogden, E., and Southard, F. D., Jr. Renin-Like Substance in Blood After Hemorrhage, *Proc Soc Exper Biol & Med* **48**: 505-508, 1941.

15 Collins, D. A., and Hamilton, A. S. Changes in the Renin-Angiotonin System in Hemorrhagic Shock, *Am J Physiol* **140**: 499-512, 1944.

16 Page, I. H. The Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage and Burns, *Am J Physiol* **139**: 386-398, 1943.

pressures were studied according to the method described. The results are shown in table 7 and in the chart. Studies of blood from 7 other normal patients were also made. These will be referred to again as the individual patient controls in connection with the angiotonin-treated group.

Analysis of the data on the vasoconstrictor effect of ultrafiltrates of citrated plasma from 5 patients with normal blood pressures presented in table 7 shows individual variation. The pres-

even with calcium-free citrated frog Ringer solution plus the slight amounts of vasoconstrictor substances in normal plasma. It should be emphasized that the amount of the decrease and the suddenness with which it occurs after return to frog Ringer solution from plasma ultrafiltrate is not at all characteristic of the effects of angiotonin in calcium-free citrated frog Ringer solution or in plasma ultrafiltrates.

The average effects of the ultrafiltrates from both the first and the second 200 cc bleeding from 5 patients with normal blood pressures for four different two minute perfusion intervals are shown graphically in the chart. These curves will be commented on later.

*II Effect of Ultrafiltrates of Plasma from Patients with Hypertension*—Nine patients with hypertension were studied according to the methods described. This study represents the perfusion of 14 frogs with ultrafiltrates from hypertensive patients, inasmuch as two different 200 cc specimens of blood were obtained from most of these 9 patients. The data are shown in table 8.

An extensive number of experiments with angiotonin in calcium-free citrated frog Ringer solution and in ultrafiltrates of blood to which angiotonin had been added, referred to in other tables, have demonstrated that the vasoconstrictor effect of angiotonin was always partially or completely reversed by immediately subsequent perfusion with calcium-free citrated frog Ringer solution. In these studies on ultrafiltrates of blood plasma, therefore, we have believed it justified to demand that any decrease in perfusion rate apparently produced by an ultrafiltrate must return significantly in the direction of the control level before we can attribute a decrease of volume during the ultrafiltrate perfusion to angiotonin.

If the data in table 8 are analyzed, it may be seen that in practically no instance was there any greater decrease in perfusion volume from the ultrafiltrate from either the first or the second 200 cc sample obtained from the 9 hypertensive patients studied than was produced by ultrafiltrates of plasma from patients with normal blood pressures.

The slight decrease in perfusion volume that did occur is probably due to a well demonstrated tendency of a slight decrease to occur with time in all of these experiments. This decrease is probably due to the absence of protein in the perfusion fluids and the consequent loss of fluids from the vascular channels as well as to the slight amount of vasoconstrictor substances in all plasma. This explanation is supported by the invariable finding of edema of the various

TABLE 7—Effect of Ultrafiltrates of Citrated Plasma from Patients with Normal Blood Pressures

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals

(Each column represents the perfusion of a different frog)

Patient	L H	A R R	S F	L H H	S O
Date	5/31/44	6/6/44	6/9/44	6/15/44	6/30/44
Blood pressure	115/60	110/70	94/62	120/80	110/10
Control	100	94	121	74	42
perfusion	100	89	124	74	44
buffered	92	94	120	74	42
calcium free	90	103	112	72	48
citrated frog	90	107	111	75	46
Ringer solution	92	103	109		47
		102	106		
		99			
Perfusion with	103	98	105	78	54
ultrafiltrate	90	81	92	72	40
from first 200 cc	92	65*	80	68	39
sample	90	56	70	59	38
		45	70	52	38
Buffered frog	78	53 104	61 54	42 108	26 134
Ringer solution	81	43 107	59 70	41 106	22 113
	84	42 96	64 84	46 108	20 106
	78	39† 102	62 82	50† 106	22 106
	80	43 103	67 83	49 101	25 94
		45 102	64 87	46	24
		40	64	46	22
					20
					22
Perfusion with		112	88	113	130
ultrafiltrate		111	82	99	120
from second		109	76	93	112
200 cc sample		105	64	88	
			59		
Return to frog		91	44	82	113
Ringer solution		95	42	86	102
		99	46	92	94
		99	47	94	93
		97	47	91	91
		101	45	88	91
		96	46	90	88
			45		86
					90
					86
					90
					84

\* Severe swelling of abdomen

† Cannula moved

‡ Fluid bloody

ence of slight amounts of vasoconstrictor substances in ultrafiltrates of normal plasma is suggested by the data. In general, however, there is only very slight decrease in the volume of perfusate within the first six minutes of the perfusion. As a matter of fact, in some instances there was a slight increase in the perfusion volume for the first four minutes in the ultrafiltrates from both the first and the second 200 cc specimen. The slight decrease thereafter is thought to be due to the normal trend of perfusion volumes to decrease slightly with time,

tissues with the passage of perfusion time and by the greater decrease with plasma ultrafiltrates than with calcium-free citrated frog Ringer solution

Study of the curves in the chart are revealing. It should be understood that these curves represent averages of values obtained from the various groups of patients studied. While there are some variations in the curves for the first two minutes, we believe it highly significant that the curves obtained from plotting the data from the first

hypertensive patients do not contain any more vasoconstrictor substances than do ultrafiltrates of plasma from patients with normal blood pressures. The curves representing the effects of plasma ultrafiltrates from normal and from hypertensive patients are different from curves representing the effect of a known angiotonin solution either in calcium-free citrated frog Ringer solution or in an ultrafiltrate from blood to which angiotonin had been added. This permits the conclusion that the vasoconstrictor sub-

TABLE 8—Effect of Ultrafiltrates of Plasmas from Patients with Hypertension

	Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals													
Patient	G S		H P	A L	F F		A W		N R		L H		C H	M W
Blood pressure	200/100		190/120	285/165	192/96		200/100		184/120		240/150		200/125	250/150
Date	5/12/44		5/14/44	5/15/44	5/19/44		5/23/44		5/27/44		7/7/44		5/6/44	3/16/44
Frog	No 1	No 2	No 3	No 4	No 5	No 6	No 7	No 8	No 9	No 10	No 11	No 12	No 13	No 14
Perfusion with buffered frog	53		151	46	78		68		80		117		76	44
Ringer solution containing sodium citrate, pH 7.75	54		141	56	78		67		82		103		82	55
	55		138	62	79		67		86		107		79	64
	57		140	65	79		66		83		103		81	56
	59		148	67	78		65		83		106		82	56
	61		142	63			64		86		110		78	74
	63		146						84		110			74
			154											73
Perfusion with ultrafiltrate from first 200 cc sample, pH 8.28	61		146	67*	70		59		84		111		94	58
	62		140	76	70		68		66		112		74	53
	60			80	64		63		60		106		74	56
	58			73	60		59		54		106		56	82
	53				58		54		51		98		42	78
	50						52		47				50	
Perfusion with buffered frog	49	137		69	59	98	51	103	46	80	94	119	28	46
Ringer solution containing 0.4% sodium citrate, pH 7.75	50	130		64	60	112	48	110	50	87	93	115	30	46
	47	151		68	60	113	50	111	59	87	90	104	30	44
	52	154		76	63	117	50	110	59	93	94	103	28	46
	50	155		78	64	113	51	116	59	95	95	103	295	49
	50	165		80	64	115	51	106	59	95	98	101	295	
	50	152			64		51	104	58	93	102		30	
	50	170			65		52							
Ultrafiltrate from second 200 cc sample, pH 8.43		166	142	79†		107		106		87		104	42	
		144	128	78		102		94		69		84	45	
			127	70		106		90		55		86	42	
			118	65		100		84		52				
			‡	56		92				49				
										44				
Perfusion with buffered frog	136	124	48		93		82		34		80			
Ringer solution containing 0.4% sodium citrate	144	156	48		935		71		34		89			
	142	180	49		93		66		37		93			
	146	174	49		93		68		36		97			
	149	168	46		95		76		37		99			
	145		49				68		37		102			
	149		47				70		35		101			
							68		34					

\* Ultrafiltrate 2

† Ultrafiltrate 1

‡ Temperature 30 below control

200 cc sample from one group of 4 normal patients and from another group of 6 normal patients (into whom angiotonin was then injected) are practically identical with the curves obtained from plotting the data obtained from perfusion of 14 frogs with plasma ultrafiltrates from patients with hypertension. These curves do not differ essentially from the curve obtained from plotting the ultrafiltrates of the second 200 cc blood sample from 4 patients with normal blood pressures.

We believe, therefore, that we are justified in concluding that ultrafiltrates of plasma from

stance in ultrafiltrates of plasma from normal and from hypertensive patients is probably not angiotonin.

*III Effect of Ultrafiltrates of Plasma from Patients Whose Blood Pressures Had Been Raised by Intravenous Injections of Angiotonin*—Table 9 presents certain pertinent data which should be consulted in the interpretation of the results presented in table 10 which records the findings in the perfusion of blood ultrafiltrates obtained from patients shown in table 9.

Study of the data in table 9 shows that intravenously administered angiotonin invariably pro-

duced a rise in blood pressure in the human subject. The amount of the elevation was fairly uniform. Seven to 10 cc of angiotonin given intravenously, particularly in one dose, raised the blood pressure from the usual 120 systolic and 70 diastolic to 180 to 190 systolic and 110

six to eight minutes being the approximate duration of the elevation resulting from one injection. As previously stated, the specimens of blood were taken very rapidly with an evacuated bottle, in one to two minutes, at the peak of the elevation of blood pressure.

TABLE 9—Effects on Blood Pressures and the Duration of the Elevation of Blood Pressures of Intravenously Injected Angiotonin

Patient	Date	Initial Blood Pressure	Blood Pressure Peak Due to Angiotonin	Amount of Angiotonin Injected Intravenously	Time for Blood Pressure Rise to Peak, Minutes	Duration of Rise, Minutes
B C	3/12/44	124/84	174/110	5 cc in divided doses	9	16 (amebic dysentery)
A J	4/13/44	132/89	186/144	8.9 cc in divided doses	12	29 (diabetes)
G M	4/17/44	136/94	180/116	7 cc (in 5 and 2 cc doses)	4	8
C J	5/6/44	130/68	210/140, 230/110	17 cc (1 dose)	3	8
C C J	5/9/44	120/80	200/114	10 cc (1 dose)	4	9
J C	5/16/44	110/70	150 systolic	10 cc (1 dose)	2	6
A C	5/19/44	122/72	193/110	15 cc (1 dose)	3	7
A D	5/25/44	120/72	190/100	10 cc (two 5 cc doses)	4	7

TABLE 10—Effects on the Perfusion Rate of Ultrafiltrates of Blood Plasma from Patients with Normal Blood Pressures and from Blood Plasma Obtained During the Peak of the Elevation of Blood Pressure Due to Intravenously Injected Angiotonin

Figures Represent Cubic Centimeters of Perfusate in Consecutive Two Minute Collection Intervals										
Name	B C	G C M	A J	O J	C C J	J C	A C	A C D		
Blood pressure peak due to angiotonin intravenously	174/119	180/116	186/144	230/119	200/114	150/7	193/110	190/100		
(Each column represents the perfusion of a different frog)										
Perfusion rate	42	47 59	14 59	119 96	162 92	192 189	78 99	96 196		
with calcium free	48	54 52	15 30	130 103	160 100	116 182	84 109	92 110		
citrated frog	44	46 52	17 20	149 103	164 101	111 180	99 96	86 199		
Ringer solution	44	69 49	16 20	142 106	164 100	189	92 94	88 112		
	46	55 49	15 18	147 107	164 98	129 184	93 95	76 112		
				146 198	166	119	95 91	73 108		
				118		129	98	75		
				126			96	76		
				110						
				114						
				126						
	A*	C A	C A	C A	O A	O A	O A	O A		
Perfusion rate	22	55 50	29 32	124 118	166 98	123 150	89 88	77 111		
with ultrafiltrate	22	62 48	48 30	117 95	176 44	120 140	79 75	74 110		
from plasma	16	60 44	62 26	120 84	160 50	112 120	69 64	78 93		
obtained at peak	20	60 40	50 26	72	50	108	68 61	72 84		
of rise of blood	12	48	22	63	46		68 57	56		
pressure due to		38	20	61	42		55	44		
angiotonin			17							
			18							
			16							
			13							
Perfusion rate	22	45 25	50 06	110 60	150 38	105 112	69 51	35 73		
with frog Ringer	24	49 28	30 04	115 75	162 42	110 117	67 52	28 76		
solution repeated	22	32 34	20 02	140 88	144 47	113 120	72 56	36 78		
	22	29 28	20 02	158 94	152 50	117 127	70 56	78		
	26	26	18	158 104	150 60	124 140	71 56	38 80		
	49	21		161 104	66	127 134	68 59	36 80		
	48			164 116	76	132	66 54	36 74		
	48			158 110	79	122	63 57	39 74		
	42			156 118	78	125	55	40 68		
	42			155 122	87		59	66		
	46			148 118	90					
				145 130	104					
				146	94					

\* C indicates control plasma, 1st 200 cc sample, A indicates angiotonin plasma, 2d 200 cc sample, while blood pressure was elevated by angiotonin.

to 140 diastolic. The patient J C is an exception. Ten cubic centimeters of angiotonin raised his pressure from 110 systolic and 70 diastolic only to 150 systolic. The elevation in pressure is rapid, two to four minutes being required to reach the peak, and the fall is fairly rapid,

Table 10 contains the results of perfusing frogs with ultrafiltrates of the plasma from 8 patients in whom the blood pressure had been raised by intravenous injections of angiotonin. With the exception of patient B C, each of the 7 others had two different bleedings of 200 cc each

from the femoral artery. The first 200 cc was taken immediately before and the second 200 cc was taken during the peak of the rise in blood pressure due to intravenously administered angiotonin. Ultrafiltrates were made from the citrated plasma obtained from each bleeding. The effects on the perfusion rates of the two ultrafiltrates were noted by comparing the rates with those of ultrafiltrates from another group of normotensive patients in whom angiotonin was not injected.

The data in table 10 can be summarized by saying that perfusion of frogs with the ultrafiltrates from the plasma of the first 200 cc control sample from 8 patients had a slight vasoconstrictor action. This has been previously called attention to in table 7, which contains the data on other patients with normal blood pressures. The slight decrease in rate of perfusion is attributed to vasoconstrictor effect, because the perfusion rate generally increased to or toward previous levels when the ultrafiltrates were followed by calcium-free citrated frog Ringer solution.

The ultrafiltrates from blood samples taken during the peak of the rise in blood pressure due to angiotonin, on the other hand, produced a decided drop in perfusion rates. This drop was manifested immediately and abruptly. The perfusion rate always returned toward or nearly to the preultrafiltrate rates when perfusion with calcium-free citrated frog Ringer solution followed perfusion with these ultrafiltrates.

Examination of the curves in the chart and of the tables which present data obtained from perfusion of ultrafiltrates of plasma from normal or hypertensive patients shows a considerable and abrupt fall in perfusion rates for the first two minute interval after the resumption of perfusion with calcium-free citrated frog Ringer solution. We are unable to explain this rather characteristic finding in the groups referred to. It may be due to technical factors or, it may be due to sudden swelling of capillary endothelium owing to the difference in the composition of the two fluids. It is noteworthy that this fall did not occur after the perfusion of any of the fluids or ultrafiltrates containing angiotonin.

The chart shows graphically the results discussed. The sharp and extreme fall produced by perfusion of ultrafiltrates of blood taken at

the peak of the rise in blood pressure due to angiotonin given intravenously is in pronounced contrast to the effects of plasma ultrafiltrates from normal and from hypertensive patients.

#### SUMMARY

A method for the bioassay of vasoconstrictor substances in ultrafiltrates of citrated plasma has been devised. With adequate control studies, ultrafiltrates of blood plasma from patients with normal blood pressure, with essential hypertension and with elevation of blood pressure produced by angiotonin have been bioassayed for vasoconstrictor substances. Ten tables and one graph presenting the results were prepared.

#### CONCLUSIONS

The vasoconstrictor effect of angiotonin can be detected in perfusions of whole pithed frogs.

Angiotonin may be ultrafiltered and detected in blood plasma ultrafiltrates by this method of bioassay.

Angiotonin may be demonstrated in the ultrafiltrates of plasma from patients whose blood pressures have been elevated by intravenous injections of angiotonin.

Ultrafiltrates of blood plasma from normal and from hypertensive patients contain an almost identical amount of vasoconstrictor substance or substances.

Ultrafiltrates of blood plasma from patients made transiently hypertensive by angiotonin contain a much greater amount of vasoconstrictor substance than ultrafiltrates of plasma from hypertensive patients whose blood pressures are much higher.

Plotted curves of vasoconstrictor effects of ultrafiltrates of plasma from normotensive and from hypertensive persons are identical and differ greatly in character from curves of vasoconstrictor effects of angiotonin in frog Ringer solution or in ultrafiltrates of blood plasma to which angiotonin has been added.

Angiotonin is not present in increased amounts in the blood of patients with essential hypertension of long duration.

In essential hypertension of long duration, the elevation of blood pressure is not due to increased production of angiotonin. Essential hypertension is probably not caused by an increased production of angiotonin.

# OPTIMUM DOSE OF SULFADIAZINE IN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

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Extensive experience with the sulfonamide drugs in clinics throughout the United States has established sulfadiazine as the drug of choice in the treatment of pneumococcic pneumonia because of its greater efficacy and lower toxicity.<sup>1</sup> Hence it is important to establish its optimum

dose in order that it may be used with maximum effectiveness

The initial dose of sulfadiazine usually advocated is 4 or 5 Gm.<sup>2</sup> However, it varies from 2<sup>3</sup> to 7<sup>11</sup> Gm. A maintenance dose of 1 Gm every four hours is usually given,<sup>4</sup> although 1 Gm.<sup>5</sup> or 2 Gm.<sup>11</sup> every six hours have also been used. It has been demonstrated<sup>11</sup> that, since sulfadiazine is excreted slowly, a proportionately higher dose given every six hours is as effective in maintaining adequate blood concentrations as is a four hourly dose.

Early in the use of sulfadiazine, its administration by the intravenous route was reserved for critically ill patients and for patients who could not take medicaments<sup>6</sup> orally. More recently, however, the administration of 5 Gm of sodium sulfadiazine intravenously as soon as the diagnosis of pneumococcic pneumonia is made has been recommended for all patients who are moderately or severely ill. This is to be repeated

Martha C. Eaton, A.B., aided in compiling statistical data

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4 (a) Billings, F. T., Jr., and Wood, W. B., Jr. Studies on Sulfadiazine. III The Use of Sulfadiazine in the Treatment of Pneumococcal Pneumonia, *Bull Johns Hopkins Hosp* **69** 314 (Oct.) 1941. (b) Browne, S. M., Marvin, H. P., and Smith, E. R. Sulfadiazine Pneumonia Therapy in Canal Zone (with Especial Reference to Bradycardia), *Dis of Chest* **9** 297 (July) 1943. (c) Sulfadiazine, report of the Council on Pharmacy and Chemistry, *J. A M A* **118** 730 (Feb 28) 1942. (d) Flippin and others<sup>1a</sup> Finland, Strauss and Peterson<sup>1b</sup> Dowling and others<sup>1c</sup> Shackman and Bullova<sup>1j</sup> Samper and Finland<sup>1o</sup> Volini and others<sup>2a</sup> Jeck and Orkin<sup>3a</sup> Flippin, Schwartz and Domm<sup>1e</sup>

5 Flippin, Schwartz and Domm<sup>1e</sup> Shackman and Bullova<sup>1j</sup>

6 Flippin and others<sup>1a</sup> Finland, Strauss and Peterson<sup>1b</sup> Dowling and others<sup>1c</sup> Flippin, Schwartz and Domm<sup>1e</sup> Shackman and Bullova<sup>1j</sup> Billings and Wood<sup>4a</sup>

if, for any reason, adequate dosage cannot be maintained by oral medication.<sup>7</sup> It has been pointed out that intravenous administration of the initial dose starts therapy at once,<sup>8</sup> avoiding the delay of four to eight hours required for the absorption of sulfadiazine given orally.<sup>9</sup> Peterson and Finland<sup>11</sup> stated that sulfadiazine is erratically absorbed in sick and toxic patients and that therapeutic levels may be difficult to reach in such patients by oral medication alone.

Blood concentrations of sulfadiazine with usual doses vary from 5 to 10 mg per hundred cubic centimeters.<sup>10</sup> It has been recommended that the blood level be maintained between 8 and 12 mg,<sup>11</sup> 8 and 15 mg<sup>11</sup> or 8 and 10 mg<sup>2a</sup> and at no less than 10 mg in moderately ill patients and between 15 and 20 mg in severely ill patients.<sup>11</sup>

Although Dowling and his associates<sup>12</sup> entitled their study "The Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcic Pneumonia," they actually compared usual doses with low doses. They did not use more than the usual dose (4 to 5 Gm initially and 1 Gm every four hours thereafter) at any time. The low dose consisted of 2 Gm initially and 0.5 Gm every four hours thereafter. They found no significant difference between the mortality rates in these two groups. The group receiving the lower dose had a higher morbidity and had almost 50 per cent more complications than the

group receiving the higher dose. The only conclusion that can be drawn from this study is that doses smaller than the usual are not so effective.

Frisch, Price and Myers<sup>7a</sup> found that lower than usual doses for mildly ill patients with pneumonia, having sputum counts of less than 35 pneumococci per oil immersion field, resulted in a higher incidence of relapses and complications.

Marangoni and D'Agati,<sup>13</sup> in treating meningococcic infections, gave 25 Gm of sulfadiazine during the first twenty-four hours and 12 to 15 Gm daily thereafter, maintaining blood levels of from 15 to 20 mg per hundred cubic centimeters. By such a regimen they obtained a mortality rate among the patients thus treated of only 31 per cent. After contrasting their results with the usual 10 per cent mortality rate reported in the literature, they recommended the use of massive doses of sulfadiazine in the treatment of meningococcic infections.

Browne<sup>4b</sup> noted 1 death in 100 consecutive patients with pneumonia who obtained high blood levels of sulfadiazine from 8 to 30.8 mg per hundred cubic centimeters. Frisch, Price and Myers<sup>7a</sup> reported on a group of patients (classed as severely ill) with sputum counts between 36 and 50 pneumococci per oil immersion field who were given double the routine dose (4 Gm intravenously and 4 Gm orally, then 2 Gm every four hours thereafter). The mortality rate in this unfavorable group, only 9 per cent, they ascribed to the use of "intensive chemotherapy." Patients classed by them as having "overwhelming pneumonia," with sputum counts over 50 per oil immersion field, who received the usual dose (4 Gm initially followed by 1 Gm every four hours) had a mortality rate of 79 per cent. In a similar group who received double this dose the mortality rate was 42 per cent. The conclusion reached by these investigators was that "massive doses of sulfonamide intravenously offer a greater chance of survival" and that "it is possible even larger doses might be more effective when the sputum count exceeds 50 per field."

In a group of patients previously reported on<sup>11</sup> it was found that the maintenance of higher sulfadiazine blood levels reduced the gross mortality. In that study it was frequently observed that patients would have large numbers of pneumococci in the sputum and active spread of

7 (a) Frisch, A. W., Price, A. E., and Myers, G. B. Pneumococcic Pneumonia. The Selection and Control of Serum and Chemotherapy by Sputum Examinations, *Am J M Sc* **205** 771 (June) 1943. (b) Collen and Dybdahl.<sup>11</sup> Shackman and Bullowa.<sup>13</sup> Peterson and Finland.<sup>11</sup>

8 Collen and Dybdahl.<sup>11</sup> Volini and others.<sup>2a</sup> Frisch, Price and Myers.<sup>7a</sup>

9 (a) Reinhold, J. G., Flippin, H. F., Schwartz, L., and Domm, A. H. The Absorption, Distribution, and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, *Am J M Sc* **201** 106 (Jan) 1941. (b) Peterson, O. L., Strauss, E., Taylor, F. H. L., and Finland, M. Absorption, Excretion and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), *ibid* **201** 357 (March) 1941. (c) Samper and Finland.<sup>10</sup>

10 Flippin and others.<sup>1a</sup> Dowling and others.<sup>1c</sup> Finland, Peterson and Goodwin.<sup>1c</sup> Shackman and Bullowa.<sup>13</sup> Dowling and others.<sup>1a</sup> Samper and Finland.<sup>10</sup> Volini and others.<sup>2a</sup> Jeck and Orkin.<sup>3a</sup> Reinhold and others.<sup>9a</sup> Peterson and others.<sup>9b</sup>

11 Lowell, F. C. The Present Status of Sulfonamide Therapy, *M Clin North America* **27** 1247 (Sept) 1943.

12 Dowling, H. F., Hartman, C. R., Feldman, H. A., and Jenkins, F. A. The Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcic Pneumonia, *Am J M Sc* **205** 197 (Feb) 1943.

13 Marangoni, B. A., and D'Agati, V. C. Treatment of 134 Cases of Meningococcic Infection with Massive Doses of Sulfadiazine, *Am J M Sc* **207** 67 (Jan) 1944.

pneumonia with the usual doses of sulfadiazine but would show prompt improvement with an increase in the dosage of the drug. This observation prompted the present clinical study.

Gross mortality statistics for pneumonia have little comparative value, since so many variable factors are involved in determining the severity of pneumonia in an individual patient. No 2 cases or series of cases can be directly compared unless they represent conditions of approximately equal severity.

The mortality rates of pneumococcal pneumonia treated with sulfadiazine and specific antisera in large series of reported cases vary from 7.6 per cent (Billings and Wood<sup>14</sup> in a series containing fewer patients with bacteremia and more patients treated early in the course of the disease) to 14.3 per cent (Shackman and Bullowa<sup>15</sup> in a series containing a higher percentage of older patients). The average mortality rate with sulfadiazine therapy in the larger series reported is approximately 10 per cent.<sup>14</sup>

Because the series reviewed does not necessarily represent cases of pneumonia of equal severity, the gross statistics are of value only in a general way in indicating success of treatment.

#### OUTLINE OF CLINICAL STUDY

It is the purpose of this study to compare results for two series of patients, in whom the disease was similarly severe, cared for in the same hospital by the same staff and treated with the same general therapeutic routine, except that the first group received the usual doses of sulfadiazine while all moderately and severely ill patients in the second group received double the usual dose.

The diagnosis of pneumonia was substantiated in every case by positive roentgenographic evidence. No patients with "minimal pneumonia," "pneumonitis" or similar indefinite diagnoses were included in either series. Patients with pneumonia as a contributory diagnosis to another primary illness were excluded.

From September 1942 through August 1943, 618 patients with pneumococcal pneumonia were treated at the Permanente Foundation Hospital.

14 (a) Collen, M. F., Dybdahl, G. L., and O'Brien, G. F. A Study of Pneumonia in the Shipbuilding Industry. The Epidemiology and Management of 864 Cases over a One-Year Period in the Kaiser Richmond Shipyards, *J. Indust. Hyg. & Toxicol.* **26**: 1 (Jan.) 1944.  
(b) Flippin and others<sup>11</sup>; Finland, Strauss and Peterson<sup>12</sup>; Dowling and others<sup>13</sup>; Smith<sup>14</sup>; Finland, Peterson and Goodwin<sup>15</sup>; Bortz<sup>16</sup>; Flippin, Schwartz and Domm<sup>17</sup>; Dowling and Lepper<sup>18</sup>; Reimann<sup>19</sup>; Dowling and others<sup>20</sup>; Volini and others<sup>21</sup>.

The majority of this group received 4 or 5 Gm of sulfadiazine orally as an initial dose, severely ill patients received an initial dose of 5 Gm of sodium sulfadiazine intravenously and 2 Gm of sulfadiazine orally. One gram of sulfadiazine every four hours or 2 Gm every six hours was administered as a maintenance dose. Average blood levels varied from 8 to 10 mg of sulfadiazine per hundred cubic centimeters. As is evident, this first group received the usually recommended dose of sulfadiazine.

Adjuvant therapy in the form of fluids, expectorant cough mixtures, oxygen by inhalation and specific pneumococcus serum (see table 9) was used routinely. In this group of 618 patients 66, or 10.7, per cent died.

From September 1943 through April 1944, a group of 748 patients with pneumococcal pneumonia were treated at this hospital. This group of patients received the same adjuvant therapy and general therapeutic regimen as the first group. However, every patient in this second group who was moderately or severely ill received 5 Gm of sodium sulfadiazine intravenously and 5 Gm of sulfadiazine orally (total 10 Gm) as an initial dose. This was followed by 4 Gm of sulfadiazine orally every six hours as a maintenance dose. In this group blood sulfadiazine levels were found to range from 12 to 20 mg per hundred cubic centimeters. In critically ill patients attempts were made to maintain blood sulfadiazine levels at about 20 mg or even higher. In this second group (748 patients) 46, or 6.2 per cent, died.

These results indicate that for patients with pneumococcal pneumonia higher doses of sulfadiazine (10 Gm initially and 4 Gm every six hours thereafter, producing blood levels of sulfadiazine of 12 to 20 mg per hundred cubic centimeters) resulted in a gross mortality rate of only 6.2 per cent, as compared with a mortality rate of 10.7 per cent for those treated with the usual dosage (average 5 Gm initially and 2 Gm every six hours thereafter, with blood levels of sulfadiazine of 8 to 10 mg). With no other change in therapy, doubling the dose of sulfadiazine decreased the gross fatality rate by 40 per cent of its previous figure. This confirms the report of Frisch, Price and Myers.<sup>22</sup>

#### COMPARATIVE SEVERITY OF ILLNESS IN THE TWO SERIES

Since it has been emphasized that gross mortality statistics have little comparative value unless they are for illnesses of approximately equal severity, these two groups are analyzed

as to the comparative severity of the various important factors which influence the mortality rate of pneumococcic pneumonia (tables 1 through 9)

*Age of Patients*—As is demonstrated in table 1, the age of a patient is an extremely important factor influencing mortality in pneumonia. Table 1 further shows that the comparative incidence according to age agrees very closely in the two series. It is important to

evident in table 2. The incidence of multiple lobar involvement is slightly higher in the group receiving the double dose. This factor tends to favor the group receiving the usual dose as being less severely ill on the whole. However, the double dose regimen was as effective in lowering the mortality rate in the group with multiple lobar involvement as it was in those patients with involvement of only a single lobe.

TABLE 1—Comparative Incidence by Age

Age, Years	Usual Dose				Double Dose			
	Patients, Number	Incidence per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
Under 20	35	5.7	1	2.9	49	6.6		0.0
20-29	129	20.9	5	3.9	141	18.8	3	2.1
30-39	137	22.1	9	6.6	177	23.7	5	2.8
40-49	136	22.0	25	18.4	172	22.9	10	5.8
50-59	103	16.7	16	15.5	126	16.9	18	14.3
60-69	72	11.6	10	13.9	75	10.0	9	12.0
70 and over	6	1.0	0		8	1.1	1	
Total	618	100.0	66	10.7	748	100.0	46	6.2

TABLE 2—Comparative Severity by Number of Lobes Involved

Involvement, Lobe	Usual Dose				Double Dose			
	Patients, Number	Incidence per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
Single	438	70.9	22	5.0	498	66.5	16	3.2
Multiple	180	29.1	44	20.5	250	33.5	30	12.0
Total	618	100.0	66	10.7	748	100.0	46	6.2

TABLE 3—Comparative Incidence of Specific Pneumococcic Types

Pneumo- coccic Type	Usual Dose				Pneumo- coccic Type	Double Dose			
	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent		Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
VII	68	11.0	20	29.4	VII	92	12.3	10	10.9
IV	34	5.5	5	14.7	XXV	55	7.4	1	1.8
I	29	4.7	4	13.8	I	52	7.0	6	11.5
XXV	26	4.2	3	11.5	III	47	6.3	16	34.0
II	22	3.6	6	27.3	V	45	6.0	2	4.4
VIII	16	2.6	0	0.0	VIII	32	4.3	0	0.0
XII	14	2.3	2	14.3	IV	31	4.1	4	12.9
III	11	1.8	2	18.2	XII	30	4.0	2	6.7
V	11	1.8	2	18.2	XXIV	13	1.7	1	7.7
IX	10	1.6	2	20.0	XXXII	13	1.7	0	0.0
XX	9	1.5	1		XX	11	1.5	0	
XXXIII	8	1.3	1		XXXIII	11	1.5	0	
XIV	7	1.1	1		II	10	1.3	2	
VI	6	1.0	1		XVIII	10	1.3	0	
XXIV	5	0.8	0		XIX	10	1.3	1	
Organisms typed for 311 patients Total patients, 618					Organisms typed for 532 patients Total patients, 748				

note that 51 per cent of the patients in both series were over 40 years of age and that only 6 per cent were under 20 years of age. It is of interest that in the series of patients receiving the double dose the mortality rate is lower in every decade.

*Comparative Severity According to Number of Lobes Involved*—The extent of involvement of the lungs by pneumonia is of great importance in determining the severity of the disease as is

*Comparative Incidence of Specific Pneumococcic Types*—Table 3 reveals that *Pneumococcus* type VII was in both series the most frequent etiologic organism and was encountered with approximately the same incidence. Types XXV and I were also prominent in both groups. It is important to note that illnesses caused by type III not only greatly increased in frequency in the group receiving the double dose, but almost doubled in percentage of mor-

tality This observation suggests that sulfadiazine in any dosage is of little value in the treatment of *Pneumococcus* type III pneumonia Although it is difficult to draw any conclusions from table 3, it is apparent that the same types were prominent in both groups and that a general decrease in percentage of mortality occurred in the group receiving the double dose (exclusive of type III)

*Comparative Incidence of Bacteremia*—Blood for culture was taken routinely on every patient before any sulfadiazine was administered The

table 5, a leukocyte count below 6,000 cells per cubic millimeter is a grave sign Leukocyte counts presented in this table are those taken on the patient's admission to the hospital and cannot be interpreted as being due to sulfadiazine toxicity (Leukopenia as a manifestation of drug toxicity is presented in table 12) Table 5 demonstrates that the incidence of leukopenia is identical in the two groups of patients In the group of patients critically ill with leukopenia, the double dose regimen resulted in a considerably decreased mortality

TABLE 4—*Comparative Incidence of Bacteremia*

Bacteremia	Usual Dose				Double Dose			
	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
Present	76	12.3	25	32.9	93	12.4	15	36.1
Absent	542	87.7	41	7.7	625	83.6	31	5.0
Unknown or not determined	0	0.0	0	0.0	30	4.0	0	0.0
Total	618	100.0	66	10.7	748	100.0	46	6.2

TABLE 5—*Comparative Incidence of Leukopenia*

Leukocytes per Cu Mm	Usual Dose				Double Dose			
	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
Under 6,000	34	5.5	22	64.7	42	5.6	20	47.6
6,000 to 10,000	72	11.6	13	18.3	94	12.7	9	9.6
10,000 to 25,000	376	60.9	22	5.9	455	60.9	13	2.9
Over 25,000	127	20.5	9	7.1	153	20.3	3	2.0
Unknown	9	1.5	0		4	0.5	1	
Total	618	100.0	66	10.7	748	100.0	46	6.2

TABLE 6—*Comparison of Number of Days of Illness Before Hospitalization*

Days of Illness, Number	Usual Dose				Double Dose			
	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
1	156	25.2	12	7.7	187	25.0	6	3.2
2	145	23.5	14	9.7	138	18.3	3	2.2
3 or 4	164	26.6	20	12.2	206	27.7	11	5.3
Over 4	114	18.4	15	13.2	202	27.0	24	11.9
Unknown	39	6.3	5		15	2.0	2	
Total	618	100.0	66	10.7	748	100.0	46	6.2

presence of bacteremia is an important factor influencing the mortality of pneumococcal pneumonia, as demonstrated in table 4 This table shows that the incidence of bacteremia was almost identical in the two groups of patients In patients with a positive blood culture, a great decrease in mortality rate occurred in the group treated with the double dose regimen as compared with those treated with usual doses

*Comparative Incidence of Leukopenia*—The importance of leukopenia as a prognostic factor in pneumococcal pneumonia<sup>14a</sup> is not always emphasized, but, as is clearly demonstrated in

*Comparison of Number of Days of Illness Prior to Hospitalization*—The number of days a patient is ill before his admittance to the hospital is of some importance in influencing the mortality of pneumococcal pneumonia The onset of illness was considered to be the first day on which the patient noted pain in the chest, blood-streaked sputum or chill The incidence of patients admitted after only one day of illness is the same in both groups, as shown in table 6 However, the group receiving the double dose contained a greater number of patients who were admitted late in their illness This factor tends

to favor the group receiving the usual dose as being less severely ill

*Comparative Incidence by Severity of Associated Diseases*—Obviously the presence of an associated disease may be highly important in influencing the mortality of pneumonia. The grading of the severity of an associated disease is difficult and depends on the judgment of the examiner. Some uniformity of grading was attempted by grading an associated disease as "mild" if it was sufficiently severe to aggravate or alter the course of the pneumonia, "moderate" if it was sufficiently severe so that associated

*Frequency of Use of Adjuvant Specific Pneumococcal Therapy*—Adjuvant therapy, as outlined elsewhere,<sup>11</sup> was identical in both groups. Specific pneumococcus serum was given throughout for similar indications. Five and eight-tenths per cent more patients in the group receiving the double dose received specific serum than in the group receiving the usual dose, as shown in table 9. This increased use of serum was primarily due to its liberal administration to the majority (59.6 per cent) of patients with *Pneumococcus* type III pneumonia. In all other types, the frequency with which adjuvant serum

TABLE 7—Comparative Incidence by Severity of Associated Diseases

Associated Diseases, Grade of Severity	Usual Dose				Double Dose			
	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent	Patients, Number	Incidence, per Cent	Deaths, Number	Mortality, per Cent
Present	122	19.7	17	13.9	142	19.0	15	10.6
Mild	64	52.5	4	6.2	34	36.6	2	5.9
Moderate	37	30.3	4	10.8	43	46.2	0	0.0
Severe	21	17.2	9	42.8	16	17.2	12	75.0
Total graded	122	100.0	17	13.9	93	100.0	14	15.1
Severity not graded	0	0.0	0	0.0	49	0.0	1	2.0
Not present	496	80.3	49	9.9	606	81.0	31	5.1
Total	618	100.0	66	10.7	748	100.0	46	6.2

with pneumonia it might endanger the life of the patient and "severe" if the associated disease was in itself sufficient to jeopardize the life of the patient. Table 7 shows that associated diseases were present with the same frequency in the two groups. Associated diseases graded as "severe" were present in 17 per cent of both series.

TABLE 8—Comparative Number of Deaths Occurring Within Six Hours After Admission

Time of Death, Hours After Admission	Usual Dose		Double Dose	
	Deaths, Number	Deaths, per Cent	Deaths, Number	Deaths, per Cent
Under 6	3	4.5	5	10.9
Over 6	63	95.5	41	89.1
Total	66	100.0	46	100.0

#### *Comparative Number of Deaths Occurring Within Six Hours After Patient's Admission*

Patients who die within a few hours after their admission to the hospital obviously alter mortality statistics without indicating the effect of therapy. Therefore it is important to consider this factor in comparing these two series. Table 8 indicates that over twice as many patients who died within six hours were admitted during the period when the double dose regimen was used than when the usual dose of sulfadiazine was used. By eliminating patients who died within six hours after their admission, the mortality rate of the patients treated with the usual dose is 10.2 per cent and with the double dose, 5.5 per cent.

was used differed in the two groups by only 3.7 per cent. There is no reason to believe that

TABLE 9—Comparative Frequency of Use of Adjuvant Serum Therapy

Serum	Usual Dose		Double Dose		Increase, per Cent
	Patients, Number	Incidence, per Cent	Patients, Number	Incidence, per Cent	
Type III					
Serum used	5	45.5	28	59.6	14.1
Serum not used	6	54.5	19	40.4	
Others (exclusive of III)					
Serum used	88	14.5	128	18.2	3.7
Serum not used	519	85.5	573	81.8	
All types					
Serum used	93	15.1	156	20.9	5.8
Serum not used	525	84.9	592	79.1	
Total	618	100.0	748	100.0	

this small increase in the use of serum could influence the final mortality statistics to any great degree, because it has been shown that when an adequate dosage of sulfadiazine is used little further decrease in mortality occurs with the added use of specific serum.<sup>14a</sup> The increased use of serum was as ineffectual as the increased dose of sulfadiazine (table 3) in reducing the mortality of type III *Pneumococcus* pneumonia.

14a Frisch, Price and Myers<sup>7a</sup>; Plummer, N, and Others. Chemotherapy Versus Combined Chemotherapy and Serum in the Treatment of Pneumonia. A Study of 607 Alternated Cases, J A M A **116**: 2366 (May 24) 1941.

*Summary of Factors of Comparative Severity*—Tables 1, 3, 4, 5 and 7 demonstrate that the two groups of patients are comparable and similar with reference to (1) size, (2) age incidence, (3) comparative incidence of specific pneumococcus types, (4) incidence of bacteremia, (5) incidence of leukopenia and (6) comparative severity of associated diseases

Tables 2, 6 and 8 show that the group receiving the double dose could be considered somewhat more severely ill because of (1) a higher incidence of multilobar involvement, (2) a greater number of patients admitted late in their illness and (3) a greater incidence of patients in terminal stages who died within six hours after admission. On the other hand, table 9 indicates that this group was favored by a slightly higher frequency with which adjuvant specific pneumococcus serum was used. In general these two groups of patients are remarkably similar with reference to the various factors which influence mortality in pneumococcal pneumonia. Although there are a few factors which tend to favor each group, it is reasonable and justifiable to assume that they tend to balance and will not be of great importance in influencing the final results.

It has been established that these two groups of patients are approximately equal in severity of illness, and therefore their mortality statistics can be directly compared.

#### THERAPEUTIC EVALUATION OF USUAL AND DOUBLE DOSES OF SULFADIAZINE

The evaluation of the success of therapy in pneumonia encompasses a study of the mortality rate, the incidence of complicating conditions, the length of stay in the hospital and the frequency of relapse.

*Gross Mortality Rate*—The data presented here demonstrated that in two groups of patients with pneumonia of comparable severity the gross mortality in those treated with usual doses of sulfadiazine was 10.7 per cent, while in those treated with double the usual dose it was 6.2 per cent. The corrected mortality rate, excluding patients who died within six hours after their admission to the hospital, was 10.2 per cent with the usual dose and 5.5 per cent with the double dose.

*Comparative Incidence of Complicating Conditions*—Table 10 shows that the incidence of sterile pleural effusions in the group of patients treated with the double dose regimen was only 2.7 per cent, as compared with 5.2 per cent

in the group treated with usual doses. The incidence of other important complicating conditions was equally low in both series.

*Comparative Length of Stay in the Hospital*—Excluding those who died, 65.8 per cent of patients treated with double doses had recovered from their illness and were discharged from the hospital in less than seven days, whereas only 45.0 per cent of patients treated with usual doses had a similar stay. The criteria for discharge in both groups were the same, namely, chemo-

TABLE 10—Comparative Incidence of Complicating Conditions

Complication	Usual Dose		Double Dose	
	Patients, Number	Incidence, per Cent	Patients, Number	Incidence, per Cent
Sterile effusion	32	5.2	20	2.7
Empyema	1	0.2	2	0.3
Pulmonary abscess	1	0.2	4	0.6
Meningitis	2	0.3	0	0.0
Endocarditis	1	0.2	2	0.3
Pericarditis	1	0.2	2	0.3

therapy was discontinued after twenty-four to forty-eight hours of normal temperature, and the average patient was discharged twenty-four to forty-eight hours later. Severely ill patients usually required two to four more days of convalescence. It is also noteworthy that only 8.1 per cent of patients treated with double doses required over two weeks of hospitalization, whereas 14.4 per cent of patients treated with usual doses required over fourteen days of hospital care.

TABLE 11—Comparative Length of Hospital Stay\*

Hospital Days	Usual Dose		Double Dose	
	Patients, Number	Cases, per Cent	Patients, Number	Cases, per Cent
Under 7	248	45.0	461	65.8
7 to 14	224	40.6	184	26.1
15 to 21	40	7.2	20	4.1
22 to 28	17	3.1	11	1.6
Over 28	23	4.1	17	2.4
Total	552	100.0	702	100.0

\* Fatalities are excluded from these figures.

Reliable data on the incidence of relapses are not available on the group of patients treated with usual doses, and so no comparison can be drawn.

The treatment of patients with pneumococcal pneumonia with double doses of sulfadiazine resulted in (1) a decrease in the mortality rate from 10.2 to 5.5 per cent, (2) a decrease in the incidence of pleural effusions from 5.2 to 2.7 per cent and (3) a decrease in the average

number of days in the hospital required for recovery (66 per cent required less than seven days, as compared with 45 per cent)

#### INCIDENCE OF SULFADIAZINE TOXICITY

It is important in studying the use of any drug to evaluate its toxicity. Numerous investigators have demonstrated that there are two distinct types of toxic reactions to sulfadiazine. The control of the commoner type and the prevention of such conditions as crystalluria and hematuria depend on an adequate volume of urine of sufficient alkalinity to dissolve the sulfadiazine. The problem can be easily eliminated by proper administration of alkali.<sup>15</sup> Every patient on the double dose regimen received the initial 5 Gm of sodium sulfadiazine intravenously in 500 cc of sixth-molar sodium lactate solution. (It is noteworthy that to maintain sodium sulfadiazine in solution, the  $p_H$  of sixth-molar sodium lactate solution should be 7 to 7.2.) Five grams of sodium bicarbonate was administered orally every six hours while the patient was receiving sulfadiazine. The decreased frequency of crystalluria in the group receiving the double dose was dependent on the routine use of alkali (table 12). The incidence of crystalluria and/or hematuria in this group was less than that reported by some authors<sup>16</sup> who used usual doses of sulfadiazine without administering alkali.

Reactions, listed in table 12, which are direct manifestations of sensitivity to sulfadiazine show no remarkable difference in frequency in the two groups. It is noteworthy that the incidence of the sensitivity manifestations of sulfadiazine toxicity listed in table 12 are comparable to those of other large series reported.<sup>17</sup>

#### SUMMARY

In a twenty month period 1,465 patients with pneumococcic pneumonia were treated at the Permanente Foundation Hospital. In the first half of this period 618 consecutive patients were treated with the usual doses of sulfadiazine, namely, 5 Gm initially and 2 Gm every six hours thereafter, maintaining an average blood level of 8 to 10 mg per hundred cubic centimeters. In the second half of this period 748 consecutive patients with pneumococcic pneu-

TABLE 12—Comparative Incidence of Sulfadiazine Toxicity

Toxic Reaction	Usual Dose		Double Dose	
	Reactions, Number	Incidence, per Cent	Reactions, Number	Incidence, per Cent
Crystalluria and/or hematuria	84	13.6	53	7.1
Cutaneous rash	10	1.6	10	1.3
Psychosis	7	1.1	7	0.9
Fever	2	0.3	3	0.4
Leukopenia or agranulocytosis	2	0.3	0	0.0
Hepatitis	0	0.0	1	0.1
Total (excluding urinary reactions)	21	3.4	21	2.8

monia were treated with double doses of sulfadiazine. The majority of patients in the group receiving the double dose received 5 Gm of sodium sulfadiazine in 500 cc of sixth-molar sodium lactate solution ( $p_H$  7.0 to 7.2) intravenously and 5 Gm of sulfadiazine orally (total 10 Gm) initially, followed by 4 Gm of sulfadiazine orally every six hours thereafter, maintaining average blood concentrations of sulfadiazine from 12 to 20 mg.

A comparative analysis of the various important factors influencing the mortality rate in pneumococcic pneumonia was made, with special reference to age, specific pneumococcic types, incidence of bacteremia, leukopenia, severity of associated diseases, extent of pneumococcic involvement, number of days of illness.

17 Long, P. H. Sulfonamide Compounds in the Prevention and Treatment of Wound Infection, *J. A. M. A.* **121** 303 (Jan 30) 1943. Finland, Peterson and Goodwin.<sup>18</sup> Flippin, Schwartz and Dorn.<sup>19</sup> Shackman and Bullowa.<sup>21</sup> Dowling and others.<sup>22</sup> Volini and others.<sup>23</sup>

15 Jensen, J. O., Jr., and Fox, C. L., Jr. Hydrogen Ion Concentration and the Solubility of Sulfonamides in Urine. The Relation to Renal Precipitation, *J. Urol.* **49** 334 (Feb.) 1943. Gilligan, D. R., Garb, S., and Plummer, N. Prevention of Crystalluria During Sulfadiazine Therapy. Experimental and Clinical Studies, *Proc. Soc. Exper. Biol. & Med.* **52** 248 (March) 1943. Hall, W., and Spink, W., cited by Watson, C. J., in discussion on Murphy, F. S., Kuzma, J. F., Polley, T. Z., and Grill, J. Renal Damage Due to Sulfonamides, *J. A. M. A.* **124** 800 (March 18) 1943. Fox, C. L., Jr., Jensen, O. L., Jr., and Mudge, G. H. Prevention of Renal Obstruction During Sulfadiazine Therapy, *ibid.* **121** 1147 (April 3) 1943. Gilligan, D. R., Garb, S., Wheeler, C., and Plummer, N. Adjuvant Alkali Therapy in Prevention of Renal Complications of Sulfadiazine, *ibid.* **122** 1160 (Aug 21) 1943. Gilligan, D. R., Dingwall, J. A., III, and McDermott, W. The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine, *Ann. Int. Med.* **20** 604 (April) 1944. Rohr, J. H., and Christopher, F. Administration of Alkalis in Sulfadiazine Therapy, *Surg., Gynec. & Obst.* **78** 515 (May) 1944. Ohnysty, J., and Wolfson, W. Q. Potassium Bicarbonate. An Adjunct to Chemotherapy in Pneumonia Complicating Cardiac Decompensation, *New England J. Med.* **231** 381 (Sept 14) 1944. Plummer and Wheeler.<sup>18</sup>

16 Finland, Peterson and Goodwin.<sup>18</sup> Volini and others.<sup>24</sup>

prior to hospitalization and incidence of patients admitted who died soon after. It was found that these two groups of patients had pneumococcic pneumonia of comparable severity. Adjunct therapy, including the use of specific pneumococcus serum, was similar in both groups. The only significant difference in these two groups of patients was that one group was treated with approximately twice the usual dose of sulfadiazine.

The treatment of patients with pneumococcic pneumonia with double doses of sulfadiazine resulted in (1) a decrease in the gross mortality from 107 to 62 per cent (corrected for patients dying within six hours after their hospitalization, the mortality rate decreased from 102 to 55 per cent), (2) a decrease in the incidence of sterile pleural effusions from 52 to 27 per cent and (3) a decrease in the average number of days in the hospital required for recovery (66 per cent required less than seven days, as compared to 45 per cent).

There was no greater incidence of drug toxicity in patients treated with double doses of sulfadiazine than in those treated with usual doses.

#### CONCLUSIONS

A study of two large groups of patients with pneumococcic pneumonia of comparable severity, treated similarly in every respect except that one group received double doses of sulfadiazine, demonstrated that the use of higher doses of sulfadiazine resulted in a great decrease in mortality rate, and a decrease in length of stay in the hospital, without any notable change in incidence of drug toxicity.

For severely ill adult patients with pneumococcic pneumonia, sufficiently large doses of sulfadiazine should be administered to maintain blood concentrations of at least 15 mg, with the optimum blood levels maintained preferably at about 20 mg of sulfadiazine per hundred cubic centimeters.

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# REVERSAL OF LINGUAL ATROPHIC CHANGES WITH NICOTINAMIDE THERAPY

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Description by Kruse<sup>1</sup> (1942) of the changes in the tongues of a group of adults which were reversed toward normal by the daily administration of 200 mg of nicotinamide led us to make an attempt to establish the validity of these conclusions in the prison population which we have been studying. The description of the diet used by these men has been given by Kyhos and associates<sup>2</sup> (1944), and it suggested that extreme deficiencies of nicotinic acid were not to be expected. The amounts of meat served and eaten were variable but never large. The bread used was baked in the prison and, so far as we can learn, was not made from enriched flour. The diet was not too different from what is used by a large part of the population engaged in industry or in agriculture, and therefore the observations may well be applicable to the medical evaluation of nutritional status of patients seen in any clinic.

As a first step, 102 men were selected at random and, without any warning, asked to stop work in the prison shops long enough to have their tongues inspected. None of these men were volunteers in the other experimental procedures we were engaged in at the time. From this inspection we recorded data on 30 men showing obvious changes such as Kruse has described. At the time of the first study a biomicroscope was not available. Hence all these observations are based on gross inspection only. The changes which we have studied have been listed as fissures, atrophy of filiform papillae and dental scalloping of the margin of the tongue. We did not see any of the evidences of acute pellagra. According to Kruse's classification, our subjects would probably be listed as being in stages three and four of chronic aniacinosis.

From the Department of Medicine of the University of Wisconsin

1 Kruse, H D. The Lingual Manifestations of Aniacinosis, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Milbank Mem Fund Quart* 20 262, 1942

2 Kyhos, E D, Gordon, E S, Kimble, M S, and Sevringhaus, E L. The Minimum Ascarbic Acid Need of Adults, *J Nutrition* 27 271, 1944

From among this group of 30 prisoners we were able, on request, to secure some cooperation from 23 men. They were given a daily dose of 50 mg of nicotinamide, administered and taken in the presence of one of the guards to make sure of its ingestion. The dose was maintained for a period of nineteen weeks, and observations were repeated by the same observer at the end of four, twelve and nineteen weeks. Subjective comments told of improved appetite or sense of vigor in a number of cases, but these were not consistent. A few men noted small gains in weight. There were no ill effects noted. The men knew only that they were being given pure vitamins. No other change in routine was called for.

Of the 23 men, there were 3 in whose tongues no fissures or crevices were observed. Of the remaining 20, with easily visible fissures, 3 could not be followed consistently enough to allow the result of treatment to be estimated. The remaining 17 men showed a striking degree of improvement, the fissures became shallower, and, in some cases the smaller fissures were no longer noticeable. In the period of our observation no tongue which was fissured lost all such marking. The improvement could be seen by the end of four weeks in 4 men, in 8 more it was evident by the end of twelve weeks, and in 2 more the beneficial effects were visible by the nineteenth week. Three of the men were not seen after twelve weeks, and it is not known whether the improvement occurred later, since their absence from the prison stopped their participation at that point. It was evident to us, therefore, that 14 of the 17 men with fissured tongues made significant improvement in not over nineteen weeks' use of 50 mg of nicotinamide daily.

Only 6 instances of dental scalloping were seen. One of these men was not interested in taking the nicotinamide. In 2 others the margin of the tongue failed to show any appreciable changes with therapy. In the other 3 there was distinct improvement, amounting in 2 instances to disappearance of the scalloped border.

Because of variations in cooperation in one way or another of the 23 men, our data on 9 of

them do not indicate the condition of the papillae with sufficient exactness to permit conclusions to be drawn. It is certain that at the conclusion of the experimental period the papillae were in a stage of excellent development and were numerous in all the 20 men who were observed at the nineteenth week. In fact, at this observation only 1 of them could be said to have any deficiency in the number or the development of the papillae. The appearance of the tongues in 14 men had demonstrated to us the progressive changes which could not be overlooked, advancing from virtual absence of papillae in 1 and scanty papillae in the others to a normal appearance in the whole group. We are sure that the improvement was complete in 5 men after twelve weeks and that the conditions were distinctly improved in the others by the nineteenth week.

After this period of treatment, some of the men were changed to a dosage of 100 mg of nicotinamide daily, and 4 were given riboflavin (1 mg each day). During the next few months several observations were made, but we were not convinced of any further improvement in fissures, scalloped borders or papillae.

These observations do not constitute a final appraisal of the changes in the tongue described by Kruse, but they have convinced us of the validity of several of the criteria he has suggested for the later stages of chronic aniacinosis. Furthermore, we believe that the use of a dose of 50 mg of nicotinamide is probably as effective as the larger dose used by Kruse, 200 mg. The completeness of recovery from the atrophy of substance evidenced in part by the fissures cannot be determined from our data. It may be possible that fissures can be eliminated in many cases. We are inclined to doubt this, suspecting that scars of the deeper fissures may prevent a complete restoration of the tongue to a normal state. It is also possible that there are other causes of fissuring in the tongue. Clinical experience with patients who were given large doses of nicotinamide for many months in order to test this hypothesis has contributed to this doubt. For example, a young man was seen because of extensive fissuring of his tongue of many years' standing, with burning paresthesias of the tongue. A previous clinical consultant had prescribed 200 mg doses of nicotinamide daily, which had been taken for over one year without benefit. It was then suggested that he desist from smoking, whereupon the paresthesias diminished rapidly, although the fissures were unchanged.

Apparent improvement in growth of papillae on the dorsum of the tongue with nicotinamide therapy led to a trial of this treatment in several

cases of severe anemia with atrophy of the dorsal papillae. Success in such cases justifies the use of this therapy in a large number of patients with pernicious anemia. Two cases may be summarized as follows.

E D W, a 54 year old diabetic woman, was moderately obese, suffered some symptoms of the climacteric and was hypertensive but without cardiac enlargement or renal damage. Gastric distress, fatigue and paresthesias in the legs had led the referring physician, a year before our examination, to a diagnosis of pernicious anemia and to the use of liver and iron therapy. The tongue had been fissured for about three years. It was only suggestively atrophic but was completely "bald." No free gastric acid appeared after the hypodermic administration of 1 mg of histamine phosphate. The blood contained 15 Gm of hemoglobin per hundred cubic centimeters, with 5,000,000 red blood cells per cubic millimeter. The diagnosis of pernicious anemia was therefore considered unproved. Treatment was based on dietary control of the diabetes and obesity, with use of diethylstilbestrol for the climacteric syndrome. Because the gastric discomfort which resulted and in spite of relief from most symptoms, other estrogenic materials were tried, and the patient was found to prefer a natural estrogenic substance.

After an interval of six months she returned with continued gastric discomfort and soreness of the tongue, which was unusually red in the midline and increasingly atrophic. The blood picture had changed in the previous five weeks from 10.3 to 8 Gm of hemoglobin, 3,170,000 to 1,970,000 red blood cells and 6,750 to 3,400 white blood cells. The mean corpuscular volume was 129 cu mm and the saturations index 0.93. She was given 15 unit doses of liver extract U S P daily, and on the fifth day the reticulocytes had risen from 1 to 18.2 per cent. The treatment was continued at 15 units weekly after her discharge. When reexamined three months later the blood contained 14.3 Gm hemoglobin and 5,310,000 red blood cells. The diagnosis of pernicious anemia appeared adequately confirmed.

Coincident with the resumption of the liver therapy, this patient was started on 100 mg doses of nicotinamide daily. Through an error of the pharmacist, the prescription was filled with nicotinic acid, which the patient took for six months in spite of the vasomotor disturbances before the error was detected from her report and the correct drug put into use. But by the end of three months' use of nicotinic acid, the papillae had become more numerous and the fissures shallower, and the burning of the tongue was no longer noted. By the end of one year the tongue looked essentially normal, as to both fissures and papillae. It had been established that 15 units of liver every ten days was an adequate dose but that if the interval was three weeks a relapse occurred. During this relapse, the tongue did not show regression. It appears, therefore, that atrophy of the tongue as seen in pernicious anemia is not reversible by the application of adequate doses of liver but may be reversed by nicotinic acid or nicotinamide. It is equally evident that the nicotinamide therapy did not prevent a relapse of the anemia. Observations in another case of diabetes with pernicious anemia substantiated these conclusions.

A third case was that of E W L, a 62 year old farmer with mild diabetes and generalized arteriosclerosis, who complained of epigastric distress after meals, constipation, sore tongue the previous year with relief after use of some preparation of vitamin B complex and weakness, paresthesias and clumsiness in the legs.

The tongue was atrophic and essentially devoid of papillae and had numerous fissures. Vibratory sense in the legs was greatly impaired, tendon reflexes were reduced, and motor tests showed ataxia. Roentgenographic study revealed only a small duodenal diverticulum. There was no production of free gastric acid after injection of 1 mg of histamine phosphate. The blood contained 115 Gm of hemoglobin, 3,140,000 red blood cells and 5,350 white blood cells. The mean corpuscular volume was 118 cu mm and the saturation index 0.98. During the course of eight days he was given 50 units of crude liver extract, but over the two weeks' period of observation there was no detectable rise in reticulocytes above the 0.4 per cent level. No noticeable change in red blood cells was observed. During the same interval he was given 150 mg of nicotinamide daily, which led to noticeable development of papillae on the dorsum of the tongue within the first week and further improvement in the second week, and the treatment was continued after his discharge. A routine was established with use of ferrous sulfate and hydrochloric acid for the anemia, since it was felt that the diagnosis of pernicious anemia could not be maintained in the face of a negative response to potent liver.

When he was reexamined after one month, the blood picture was somewhat improved (125 Gm hemoglobin and 3,408,750 red blood cells). The complaints were unchanged, but the papillae on the tongue were still well developed. Examination of the spinal fluid gave no evidence of syphilis or any other lesion of the spinal cord. It was concluded that this was a case of hyperchromic anemia with combined systemic disease, possibly due to prolonged multiple nutritional deficiencies. Therefore, liberal use of protein supplemented by a crude liver extract orally was continued. Further observations have been precluded by his failure to return

to the clinic. It seems fair to conclude that the nicotinamide therapy was effective in producing regeneration of papillae on the tongue in this atypical anemia, in spite of incomplete remission in the anemia.

#### SUMMARY

Observations on an unselected group of prisoners showed that nearly one third had visible evidence of atrophy in the tongue, including fissures, reduced number of filiform papillae and dental scalloping. Treatment with 50 mg doses of nicotinamide brought about striking improvement, most complete in the case of the papillae but also noticeable in the shallower fissures and decreased amount of scalloping. The application of similar therapy to 3 patients with fissures and atrophy of papillae, 2 with pernicious anemia and 1 with a similar anemia but without reticulocyte response to liver was followed by prompt improvement likewise. The improvement with therapy requires several months to become complete. It is concluded that the criteria of chronic anisocytosis proposed by Kline are valid.

The expenses of this investigation have been met in part by a special grant from the Nutrition Foundation to one of us (E. L. S.).

Mr. I. C. Breitlow, of the hospital staff at the Wisconsin State Prison, and Warden L. F. Murphy cooperated to make these observations possible. Dr. J. M. Carlisle, of the E. R. Merck Laboratory, supplied the nicotinamide and riboflavin used.

# ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE IN DIABETES

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Two recent trends in the field of diabetes make it of special interest to study the relation of diabetes to arteriosclerosis. One is the increased prominence of arteriosclerosis as a cause of death among diabetic persons. According to Joslin,<sup>1</sup> deaths from this cause have risen three-fold, while deaths from diabetic coma have dropped to one sixteenth of their former incidence. This circumstance may in part be due to the fact that many diabetic persons are now surviving long enough to experience advanced arterial changes. The second trend is the tendency of the physician to pay less attention to hyperglycemia and glycosuria in insulin-controlled cases. A higher incidence of premature arteriosclerosis under the newer regimens of liberal diets and insulin might indicate the need for a return to the previously accepted, more rigid standards of control.

It is well known that arteriosclerosis occurs with high frequency among diabetic persons. Some believe this frequency is due to the abnormal metabolic relationships found in diabetes. Other factors suggested are inadequacy of control of glycosuria, severity of the disease, obesity and the presence of coexisting hypertension. This report summarizes our observations with respect to the relations between these factors and the incidence of arteriosclerosis as manifested in peripheral vascular disease of the lower extremities.

## SCOPE OF THE WORK

Observations were made on 249 male patients attending the diabetic clinic. Data were obtained with regard to age, duration of diabetes, severity of the disease, use of insulin, adequacy of control, presence of obesity and arterial tension. The patients were carefully questioned as to the presence of intermittent claudication. The peripheral pulses of the lower extremities, including those of the femoral, popliteal, anterior and posterior tibial and dorsalis pedis vessels, were examined

by palpation. When the dorsalis pedis artery alone could not be felt, the case was not considered an instance of peripheral vascular disease. Absence of dorsalis pedis pulsation can be noted in a small percentage of normal persons, while in some instances this vessel has an atypical location. Oscillometric readings were made in about half the cases. In general, the instrument readings confirmed the observations made by palpation. Other workers have found that this method of determining the presence of peripheral vascular disease, namely by palpation of the vessels, corresponds well with other tests used for appraising the arterial circulation in the extremities.<sup>2</sup> Since arteriosclerosis may occur occasionally without signs or clinical symptoms, it is likely that in this survey some instances of arteriosclerosis have been missed.

## INCIDENCE OF PERIPHERAL VASCULAR DISEASE

*In Relation to Age*—Figures for age distribution and incidence of peripheral disease appear in table 1. Of the group as a whole, 51 per cent had peripheral vascular disease.

While the number of young diabetic persons is small, there being but 19 patients under 40 years of age, 5, or approximately one fourth, had clinically apparent peripheral vascular disease. In the 41 to 50 year age group, one third of the patients had some peripheral vascular involvement. In the age group of 51 to 60 years 42 per cent had some peripheral vascular disease. Beyond this age group there were 125 patients, of whom 63 per cent had evidence of peripheral vascular abnormality. As might be anticipated, the highest incidence was found in the oldest age group.

*In Relation to Duration of Diabetes*—In table 2 are summarized the data relating to the

2 (a) Kramer, L. I. Various Methods of Determining the Early Diagnosis of Arteriosclerosis in Diabetes, New England J. Med. **220** 278 (Feb 16) 1939.  
(b) Homans, J. Circulatory Deficiency in Relation to Medico-Legal Problems, Ann. Int. Med. **18** 518 (April) 1943.

From the Metabolism Clinic and the Peripheral Vascular Disease Clinic, Mount Sinai Hospital.

1 Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940.

duration of diabetes Of patients with known diabetes for less than three years, 41 per cent had peripheral vascular disease Among a total of 94 patients whose recognized diabetes was of less than five years' duration, 39, or 42 per cent, showed evidence of peripheral vascular disease There were 154 patients with diabetes of more than six years' duration In this group there were 89 instances of peripheral vascular disease, a percentage of 58 The table indicates the high incidence of peripheral vascular disease even among those patients in whom the diabetes is not long established

Observations similar to ours are reported by other workers In a roentgenologic study of the extremities of diabetic patients, Bowen, Koenig and Viele<sup>3</sup> found evident arteriosclerosis in the vessels of the legs in 50 per cent of their patients In reports by Morrison and Bogan,<sup>4</sup> Shepardson,<sup>5</sup> Kramer,<sup>2a</sup> Kramer,<sup>6</sup> Dry and Hines,<sup>7</sup> Meyers and Altschuler<sup>8</sup> and Eisele,<sup>9</sup> the incidence of peripheral vascular disease in diabetic persons

TABLE 1—Peripheral Vascular Disease in Various Age Groups

Age Group	Total No of Patients	P V D Absent	P V D Present
Under 30 years	9	7	2
31 to 40	10	7	3
41 to 50	32	21 (66%)	11 (34%)
51 to 60	73	42 (58%)	31 (42%)
Over 61	125	46 (37%)	79 (63%)
Total	249	123 (49%)	126 (51%)

ranged from 17 per cent to as high as 68 per cent Hines and Barker<sup>10</sup> found that among 280 general patients with arteriosclerosis obliterans one fifth had diabetes Wilder,<sup>11</sup> reporting on obser-

vations made at necropsies of diabetic patients under 40, found that arterial occlusion sufficient to cause symptoms was present in 39 per cent of the cases

*In Relation to Severity of Diabetes*—Our patients were classified into three groups according to the severity of the disease mild, moderately severe and severe diabetes In the group

TABLE 2—Peripheral Vascular Disease in Relation to Duration of Diabetes

Years' Duration	Total No of Patients	P V D Absent	P V D Present
Under 3	66	39 (59%)	27 (41%)
4 to 5	28	16 (57%)	12 (43%)
6 to 10	70	29 (41%)	41 (59%)
11 or more	84	36 (43%)	48 (57%)

with mild diabetes were those whose blood sugar levels were not appreciably elevated and who required no insulin or required only amounts up to 15 units Most required no insulin The patients in the group with moderately severe diabetes required from 15 to 45 units Patients who required amounts of insulin larger than this were considered to have severe diabetes

The data given in table 3 indicate no relation between the incidence of peripheral vascular disease and the severity of the diabetes Among those with mild and moderately severe diabetes the incidence of peripheral vascular disease was equally distributed When those with moderately severe and those with severe diabetes were grouped together, there were 54 instances of peripheral vascular disease, or 49 per cent, as compared with 54 per cent for those with mild diabetes Other authors<sup>12</sup> also found no relation

TABLE 3—Severity of Diabetes and Peripheral Vascular Disease

Severity of Disease	Total No of Patients	P V D Absent	P V D Present
Mild	137	63 (46%)	74 (54%)
Moderately severe	82	37 (45%)	45 (55%)
Severe	29	20 (69%)	9 (31%)

between the severity of diabetes and the extent of peripheral vascular disease

*In Relation to Degree of Diabetic Control*—Persistent glycosuria with significant elevation of the blood sugar was considered poor control, freedom from glycosuria was considered good control, while fair control included intermittent glycosuria

12 Shepardson<sup>5</sup> Meyers and Altschuler<sup>8</sup>

3 Bowen, B D, Koenig, E C, and Viele, A A Study of the Lower Extremities in Diabetes, Bull Buffalo Gen Hosp 2 35 (April) 1924

4 Morrison, L B, and Bogan, I K Calcification of the Vessels in Diabetes, J A M A 92 1424 (April 27) 1929

5 Shepardson, H C Arteriosclerosis in the Young Diabetic, Arch Int Med 45 674 (May) 1930

6 Kramer, D W Diabetic Gangrene, Am J M Sc 183 503 (April) 1932

7 Dry, T J, and Hines, E A The Role of Diabetes in the Development of Degenerative Vascular Disease, Ann Int Med 14 1893 (April) 1941

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11 Wilder, R M Diabetic Arteriosclerosis, Internat. Clin 2 13 (June) 1939

Among the 155 patients with well controlled diabetes (table 4), 78, or about one half, had peripheral vascular disease. In the less satisfactorily controlled group, or "fair," 29 out of 48 patients, or 60 per cent, had peripheral vascular disease. In the poorly controlled group, an increased incidence of occluded vessels was not found. In this group the rate was 33 per cent. The low rate among the patients with poorly controlled diabetes was not due to the fact that this group was predominantly young.

Some affirm that with better control of diabetes less arteriosclerosis is evident. White<sup>13</sup> reported the observation of arteriosclerosis, as demonstrated by roentgenographic or ophthalmologic

preventing and delaying arteriosclerosis in the lower extremities.

*In Relation to Obesity*—The factor of obesity in our patients was gaged by an appraisal of present and past weights. Some of the men were thin and of asthenic habitus and had never weighed more than 150 pounds (68 Kg). Others were obviously of heavy build and weighed more than this either previously or at the time of examination.

The incidence of peripheral vascular disease was about equally distributed as far as obesity was concerned. It occurred just as often in the nonobese as it did in the obese patients (table 5).

*In Relation to Hypertension*—Patients whose systolic tension was 150 mm of mercury or over with a diastolic pressure of 90 mm or above were classified in the hypertensive group. Those with blood pressures below these levels were regarded as nonhypertensive. The figures are given in table 6.

Sixty-seven of the nonhypertensive patients, or 49 per cent, had peripheral vascular disease, while 55 of the hypertensive group, or 56 per cent, had arterial involvement. The difference is insignificant.

TABLE 4—Control of Diabetes and Peripheral Vascular Disease

	Total No of Patients	P V D Absent	P V D Present
Good	155	77 (50%)	78 (50%)
Fair	48	19 (40%)	29 (60%)
Poor	42	28 (67%)	14 (33%)

TABLE 5—Obesity and Peripheral Vascular Disease

Type	Total No of Patients	P V D Absent	P V D Present
Never obese	87	40 (46%)	47 (54%)
Obese at time of examination or previously	160	79 (50%)	81 (50%)

TABLE 6—Hypertension and Peripheral Vascular Disease

Group	Total No of Patients	P V D Absent	P V D Present
No hypertension	138	71 (51%)	67 (49%)
Hypertension present	99	44 (44%)	55 (56%)

COMMENT

*Type and Sites of Arteriosclerotic Lesions*—The foregoing tables indicate the high incidence of peripheral vascular disease among the diabetic patients we examined. The incidence of the condition appeared to be unrelated to such factors as duration of the diabetes, severity of the disease, effectiveness of control and existence of obesity and of hypertension.

The early and apparently selective appearance of arteriosclerosis in diabetes is not limited to the vessels of the extremities. In this disorder, arteriosclerotic lesions involve other organs as well, hence peripheral sclerosis is only part of a more general picture.

Localization of arteriosclerosis in the heart and aorta is exceedingly common. This has been established on the basis of necropsies by numerous investigators, including Joslin,<sup>15</sup> Root,<sup>16</sup> Warren,<sup>17</sup> Nathan<sup>18</sup> and Root and Sharkey.<sup>19</sup> Joslin declared the heart to be the most frequent

examination or by autopsy, in 52 young diabetic persons with onset of diabetes in childhood. No sclerosis was observed when the blood sugar and blood cholesterol levels were below 200 mg. Sclerosis increased with elevation of blood cholesterol levels. In connection with these abnormal changes, hypercholesteremia appeared more significant than hyperglycemia. In the opinion of Bowen, Regan and Koenig<sup>14</sup> good control of diabetes was an influential factor in

13 White, P. Diabetes in Childhood, in Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1935.

14 Bowen, B. D., Regan, J. S., and Koenig, E. C. The Development of Arteriosclerosis in the Diabetic, Ann Int Med 12 1996 (June) 1939.

15 Joslin, E. P. Arteriosclerosis in Diabetes, Ann Int Med 4 54 (July) 1930.  
16 Root, H. F., in Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1935.  
17 Warren, S. Pathology of Diabetes, Philadelphia, Lea & Febiger, 1938.  
18 Nathan, M. H. Coronary Disease in One Hundred Autopsied Diabetics, Am J M Sc 183 495 (April) 1932.  
19 Root, H. F., and Sharkey, T. P. Arteriosclerosis and Hypertension in Diabetes, Ann Int Med 9 873 (Jan) 1936.

site of arteriosclerosis in persons with diabetes Root and Sharkey stated that coronary disease as a cause of death is four times as frequent in diabetic persons as in nondiabetic, while Nathan found coronary disease six and a half times as high

The earlier appearance of arteriosclerosis in diabetic persons as compared with its appearance in normal persons is also recognized Warren, as cited by Joslin,<sup>15</sup> Ophuls,<sup>20</sup> Lisa, Magiday, Galloway and Hart<sup>21</sup> and Lehnherr<sup>22</sup> have presented reports of necropsies in support of this fact

From the standpoint of pathologic characteristics, the actual lesion found in diabetic persons does not differ from that in nondiabetic This lack of difference has been pointed out by Ophuls,<sup>20</sup> Hines and Barker,<sup>10</sup> Lisa and others,<sup>21</sup> Sappington and Fischer<sup>23</sup> and Lisa, Magiday and Hart<sup>24</sup> The lesions consist essentially of intimal thickening, subintimal deposition of fatty material, including cholesterol, and degenerative changes in the media with a tendency to ultimate thrombosis of the vessels

*Abnormal Metabolism and Arteriosclerosis* — There is no uniformity of opinion as to what initiates these arteriosclerotic changes in diabetic patients The occurrence of marked elevation of the blood lipids in diabetes, as cited by Rabinowitch,<sup>25</sup> was long ago pointed out by Joslin, Bloor and Gray Consequently, the hypercholesteremia of diabetic patients has most frequently been held responsible for the early appearance of arteriosclerosis Emphasis on blood lipids, especially cholesterol, as specific metabolites of first importance also arose from the belief of Virchow and Aschoff that the intimal changes in arteriosclerosis represented the aging of arterial tissues through stress and strain and that fat from the blood stream was imbibed and deposited in the intima Anitschkow<sup>26</sup> experimentally produced in rabbits the typical picture of atherosclerosis by feeding them

pure cholesterol Similar experiments were extensively reported on by Leary,<sup>27</sup> who also concluded that the lesions of atherosclerosis were due to hypercholesteremia Other workers, including Bowen, Regan and Koenig,<sup>14</sup> Hines and Barker,<sup>10</sup> Rosenthal<sup>28</sup> and Rosenblum,<sup>29</sup> likewise concluded that an altered cholesterol metabolism was related to the development of arteriosclerosis

Agreement on this point does not exist Weiss and Minot<sup>30</sup> regarded as equivocal the evidence presented to demonstrate a reciprocal relation between the cholesterol content of the diet and the development of arteriosclerosis Duff<sup>31</sup> took issue with the experimental work of Leary<sup>27</sup> and cited the occurrence of arteriosclerosis in man without deviation of the blood cholesterol from normal limits Hirsch and Weinhaus<sup>32</sup> also called attention to the development of arteriosclerosis in adult life in the absence of an appreciable elevation of blood cholesterol or lipids As related to the process in diabetes, Hunt<sup>33</sup> found lowest cholesterol values in persons with greatest arteriosclerosis Among 6 juvenile diabetic patients under 20 years of age, all of whom had roentgenologic evidence of arteriosclerosis, 4 had normal cholesterol values

Winternitz expressed the opinion that the earliest changes leading to atheromatous plaque formation were due to small thrombi and hemorrhages arising in the tiny vasa vasorum of the intimal walls of vessels in which the elasticity and contractility were diminished Blumenthal, Lansing and Wheeler<sup>34</sup> have recently presented

26 Anitschkow, N Experimental Arteriosclerosis in Animals, in Cowdry, E V Arteriosclerosis, New York, The Macmillan Company, 1933

27 Leary, T Atherosclerosis, Arch Path **21** 419 (April) 1936, Experimental Atherosclerosis in Rabbit Compared with Human (Coronary) Sclerosis, *ibid* **17** 453 (April) 1934

28 Rosenthal, S R Studies in Atherosclerosis Chemical, Experimental, and Morphological, Arch Path **18** 473 (Nov) 1934

29 Rosenblum, M H A Consideration of Disease of the Blood Vessels in Diabetes Mellitus, Ohio State M J **38** 46 (Jan) 1942

30 Weiss, S, and Minot, G R Nutrition in Relation to Arteriosclerosis, in Cowdry, E V Arteriosclerosis, New York, The Macmillan Company, 1933

31 Duff, G L Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch Path **20** 81 (July) 1935

32 Hirsch, E F, and Weinhaus, S The Role of the Lipids in Atherosclerosis, Physiol Rev **23** 185 (July) 1943

33 Hunt, H M Cholesterol in Blood of Diabetics Treated in the New England Deaconess Hospital, New England J Med **201** 659 (Oct 3) 1929

34 Blumenthal, H T, Lansing, A I, and Wheeler, P A Calcification of the Media of the Human Aorta and Its Relation to Intimal Arteriosclerosis, Aging and Disease, Am J Path **20** 665 (July) 1944

20 Ophuls, W The Pathogenesis of Arteriosclerosis, in Cowdry, E V Arteriosclerosis, New York, The Macmillan Company, 1933

21 Lisa, J R, Magiday, M, Galloway, I, and Hart, J F Arteriosclerosis with Diabetes Mellitus, J A M A **120** 193 (Sept 19) 1942

22 Lehnherr, E R Arteriosclerosis and Diabetes Mellitus, New England J Med **208** 1307 (June 22) 1933

23 Sappington, S W, and Fischer, H R Arteriosclerosis Obliterans, Arch Path **34** 989 (Dec) 1942

24 Lisa, J R, Magiday, M, and Hart, J F Peripheral Arteriosclerosis in the Diabetic and the Nondiabetic, J A M A **118** 1353 (April 18) 1942

25 Rabinowitch, I M The Cholesterol Content of Blood Plasma in Diabetes Mellitus, Arch Int Med **43** 363 (March) 1929

their own material supporting the concept of numerous other workers as well that changes consisting of demonstrable calcification first occur in the medial wall and that the intimal changes with lipid deposition are secondary. Should these theories concerning the genesis and development of arteriosclerosis be correct, it is not apparent why the process should occur more prominently in diabetic persons.

Warren<sup>37</sup> stated that fluctuations in the blood sugar concentration might produce osmotic changes affecting the permeability of the intimal ground substance, thereby opening it up to deposition of lipids. Wilder and Wilbur<sup>35</sup> expressed the opinion that hyperglycemia, ketosis, frequent infections, periodic dehydration or inadequacies of the diet in certain nutritional factors might be contributory causative factors.

Moschcowitz<sup>36</sup> suggested that arteriosclerosis, differentiating it from atherosclerosis, found in diabetic patients may itself be responsible for the diabetic condition. His concept is that an arteriocapillary fibrosis in the islands of Langerhans produces the insufficiency which results in diabetes. There are few adherents to this concept, according to Lukens,<sup>37</sup> who, in discussing the pathogenesis of diabetes, stated that advanced pancreatic arteriosclerosis can exist without the presence of diabetes.

Finally, Dry and Hines<sup>7</sup> postulated a biologic background to explain the advanced arteriosclerosis in diabetic patients. They expressed a belief in an inherent weakness affecting the insulin-producing tissues and the vascular system which requires only an additional stimulus to bring out the pathologic changes in the tissues. In the case of the insulin apparatus, the stimulus can be infectious illness, overfeeding or obesity. In the case of the vascular system, the stimulus can be hypertension, obesity or lipemia.

#### SUMMARY

Of 249 male diabetic patients evidence of peripheral vascular disease was present in 51 per cent. It was found in one fourth of the patients under 40 years of age. While it was found in greater proportion in patients whose diabetes was of long standing, as many as two fifths of those with less than three years' history had some peripheral vascular disease. It occurred with equal frequency among the patients with mild diabetes and among those with more severe diabetes who used insulin. Control of the disease, reflected by minimal glycosuria, did not coincide with a lower incidence of peripheral vascular disease. Among the lean men the condition was found in the same proportion as among the obese. The slightly lower incidence in the nonhypertensive patients, 49 per cent as against 56 per cent, did not seem significant. The only apparent common denominator was the diabetic condition itself.

#### CONCLUSIONS

Confirming the work of others, our observations indicate that an apparently selective and frequently premature arteriosclerosis occurs in the peripheral vessels of the lower extremities in diabetic patients.

The increased incidence of arteriosclerosis in diabetic patients, irrespective of the usually accepted factors which determine arteriosclerosis in nondiabetic persons, may indicate a metabolic origin or imply an acceleration of the process by some metabolic factor. From the statistical standpoint of our study, the relationship between such factors and peripheral vascular disease is not made evident.

The presence of cholesterol deposits in the arteriosclerotic lesion and the hypercholesterolemia of patients with neglected or poorly controlled diabetes suggest a linkage between the two disorders. However, no such connection has so far been unequivocally established. It does not of course follow that in the treatment of diabetes such factors as control of weight and hypertension can be ignored or that suitable dietary and insulin regimens can be neglected.

35 Wilder, R. M., and Wilbur, D. L. *Diseases of Metabolism and Nutrition*, Arch Int Med 57:422 (Feb) 1936.

36 Moschcowitz, E. D. *Vascular Sclerosis*, New York, Oxford University Press, 1942.

37 Lukens, F. D. W. *The Pathogenesis of Diabetes*, Yale J Biol & Med 16:301 (March) 1944.

# EFFECT OF INTRAVENOUSLY ADMINISTERED SOLUTION OF ACACIA ON ANIMALS

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Considerable attention has been focused on intravenous administration of solution of acacia, the probable physiologic and physical action of acacia so administered and its fate in the organism. The study herein reported was a long term investigation of dogs which had received intravenously large doses of a solution of acacia similar to that used in treatment of patients who display the resistant edema that may accompany glomerulonephritis and the nephrotic syndrome. The purpose was to note the general effect on the animals as well as the specific effect on the liver

## MATERIAL AND METHODS

Three normal adult dogs, which were receiving a diet of ground raw meat, cracker meal and milk in daily amounts calculated to maintain their body weight, were used in this study. Beginning on Jan 7, 1942, each dog received intravenous injections of 6 per cent acacia in 0.06 per cent isotonic solution of sodium chloride, as is indicated in table 1. The solution was warmed to approximate body temperature, and reactions were observed after the injections. Additional amounts of acacia were injected each two or three days in order to maintain the acacia in the serum of the 3 dogs at 15, 3 and 35 per cent, respectively. Injections of acacia were discontinued after seventy-six days, on March 23.

*The Experimental Dose of Acacia Compared with the Therapeutic Dose*—In table 1 are recorded the total quantities of acacia injected into each animal. The average patient with chronic glomerulonephritis and the nephrotic syndrome who receives therapeutic injections of solution of acacia for resistant edema is given from 90 to 120 Gm of acacia, or from 1.3 to 1.8 Gm per kilogram of body weight. The doses given the animals, as recorded in table 1, represent from eight to thirty-seven times as many grams of acacia as is received by the average patient. The amounts administered to the animals are equivalent to doses of 1,068 to 3,244 Gm of acacia given to an average patient who weighs 68 Kg. Of patients with chronic glomerulonephritis and the nephrotic syndrome treated

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at the Mayo Clinic, the one who received the largest quantity of solution of acacia during the period of hospitalization was given 330 Gm, or 4.9 Gm per kilogram of body weight. This dose is much greater than the average total dose of 90 Gm divided into three injections of 30 Gm each, which is usually administered to patients. Of the 3 dogs, the 1 which received the least acacia, and in the serum of which the concentration of acacia was lowest, was given slightly more than three times the number of grams per kilogram of body weight that was given to the patient

TABLE 1—*Acacia Intravenously Administered and the Concentration of Acacia in the Blood Serum Throughout the Period of Injection*

Dog		Injec- tion Period, Days	Total Injec- tions	Total Acacia Injected, Gm	Acacia Injected per Kg Body Weight, Gm	Acacia in Serum, Average Gm per 100 Cc
Num ber	Weight, Kg					
9	64	76	32	100.6	15.7	1.4
7	70	76	35	277.8	39.7	3.0
8	58	76	35	276.6	47.7	3.4

who received the most. The dog which was given the most acacia per kilogram of body weight, and the concentration of acacia in the serum of which was maintained at the highest level, received nine and seven-tenths times the number of grams that the patient just mentioned received. This patient was living, felt well and was working daily when this paper was written. The dogs received approximately three times the number of injections of acacia given to this patient.

*Biopsy*—With the help of Dr F C Mann, abdominal exploratory operations and biopsies of the livers were performed at four different periods following discontinuance of the injections of acacia: first, at the time of completion of the administration, second, ten weeks later, third, approximately thirteen months, and, fourth, twenty-six months, after the discontinuance of the injections of acacia. Specimens for biopsy were taken from the spleens of 2 animals at the time of the last operations. At the time of these exploratory operations, the organs were inspected and specimens of tissue were obtained for chemical examination. Microscopic examination of the removed specimens was made by Dr Baggenstoss.

*Technics Employed*—The concentration of acacia in the blood serum and in the urine was determined by

precipitation of trichloroacetic acid filtrates with acetone, according to the principles of the method described by Power.<sup>1</sup> Weighed portions of tissues and stools were macerated in freshly prepared isotonic solution of sodium chloride and made up to definite volumes with trichloroacetic acid. Acacia was determined by precipitation of aliquot portions of the filtrate. Glycogen, if present in normal amounts, may be expected to interfere with an exact determination of acacia by this method. Consequently, approximate colorimetric determination of acacia present in the tissue filtrates was accomplished by application of Bial's orcin test for pentose.

Blood for analysis was obtained from the veins of the legs and by puncture of the jugular vein. When plasma was used, potassium oxalate, 5 mg per cubic centimeter, was used as an anticoagulant. Determinations of protein fractions in the blood serum were made in duplicate by Howe's method as described by Peters and Van Slyke, using 22.5 per cent sodium sulfate at 37 C. Fibrinogen was determined by the following method. Five-tenths cubic centimeter of oxalated plasma was mixed with 24 cc of 0.9 per cent sodium chloride solution and 0.5 cc of 2.5 per cent calcium chloride, and the mixture was allowed to stand overnight. The fibrin clot was removed by filtration, and 20 cc of the filtrate was analyzed for nitrogen by a modified Kjeldahl procedure. For determinations of hemoglobin, the Cenco-Sheard-Sanford photometer was used. The quantity of cells per hundred cubic centimeters was determined by centrifuging in hematocrit tubes. Mean erythrocyte determinations were made by means of the Haden-Hausser erythrocytometer.<sup>2</sup> The sulfobromophthalein sodium test was performed by Rosenthal's method.<sup>3</sup> For determination of coagulation time, the Lee and White method was employed.<sup>4</sup> The prothrombin time was determined by use of Quick's method.<sup>5</sup>

#### EXPERIMENTAL RESULTS COMPARED WITH THERAPEUTIC RESULTS

At the outset of this section of the paper, it may be advisable to explain how well, from the standpoint of tenure of life, the dogs withstood the combined experimental procedures. About three months after discontinuance of administration of acacia and after the 3 animals had recovered from two exploratory operations, 1 dog began to eat poorly, and his weight gradually decreased. He died four months after the last injection of acacia. Postmortem examination

did not reveal any specific cause of death, the liver was enlarged, but the other organs appeared normal. The other 2 animals recovered normally from four exploratory operations and were still living at the time of writing of this paper.

**Concentration of Acacia in the Blood Serum** — The average value at which the concentration of acacia was maintained throughout the period of injection in the serum of the 3 animals is given in table 1. After discontinuance of the injections, the concentration of acacia in the serum of the animals immediately began to decrease, as is

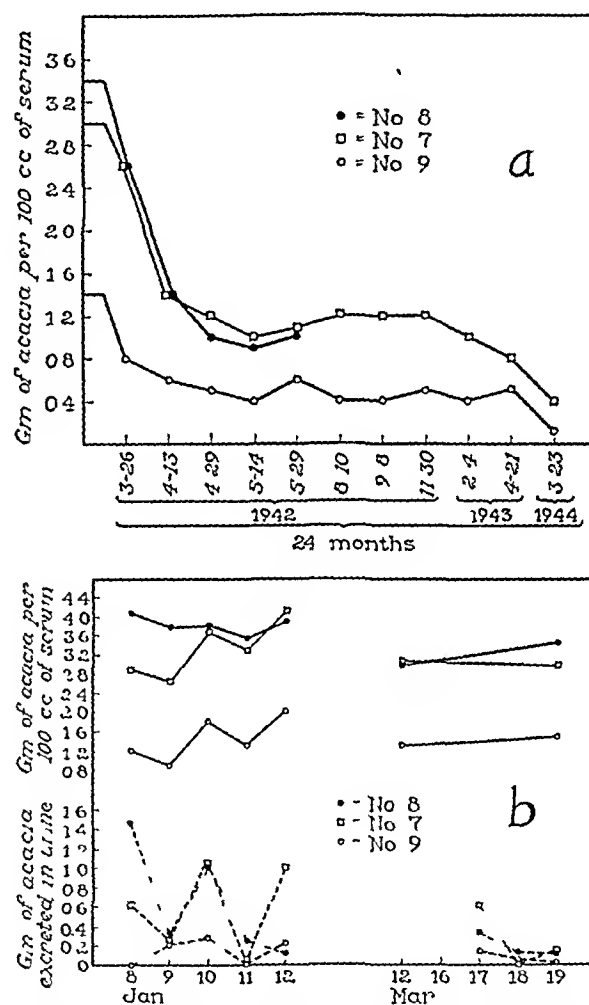


Fig 1—(a) Rate of disappearance of acacia from the blood stream. Solution of acacia was injected intravenously through a period of seventy-six days, as it was necessary to keep the concentration of acacia in the serum constant. Then injection was discontinued. The value at the extreme left of each curve represents the value at the time when injection was stopped. Values to the right were determined in the subsequent two years. (b) Concentration of acacia in the serum and quantity in the urine. Through two portions of a total period of seventy-six days, solution of acacia was injected intravenously and the indicated determinations were made. The curves at the left represent values of the first portion of the period and the curves at the right, values of the second portion. Injections were as follows: Animal 7, 21 Gm of acacia given on January 7, 9 and 11, 9 Gm on March 16. Animal 8, 34.8 Gm of acacia given on January 7 and 9, 9 Gm on March 16. Animal 9, 6.3 Gm of acacia given on January 7, 9 and 11, 3 Gm on March 16.

1 Power, M. H. A Volumetric Method for the Determination of Acacia in Serum, Lymph and Urine, abstracted, *J Biol Chem* **119** 1888-1889, 1937.

2 Haden, R. L. A New Instrument for the Diffractometric Measurement of the Diameter of Red Blood Cells, *J Lab & Clin Med* **25** 399-403 (Jan) 1940.

3 Todd, J. C., and Sanford, A. H. Clinical Diagnosis by Laboratory Methods. A Working Manual of Clinical Pathology, ed 9, Philadelphia, W. B. Saunders Company, 1939, p. 402.

4 Todd and Sanford,<sup>3</sup> p. 208.

5 Bollman, J. L., and Preston, F. W. The Effects of Experimental Administration of Dicoumarin (3,3'-Methylene-bis-[4-Hydroxycoumarin]), *J A M A* **120** 1021-1024 (Nov 28) 1942.

shown in figure 1 *a*. Two years after discontinuance of the injections of acacia, it was noted that some acacia still was present in the circulating blood, although the concentration was much reduced from that which had obtained formerly.

In the average clinical case in which the intake of fluid is controlled and in which the total dose of acacia is the average one of 90 Gm, the immediate concentration is approximately 2 Gm per hundred cubic centimeters of blood serum. When patients receive this average dose in treatment of the resistant edema of chronic glomerulonephritis and the nephrotic syndrome and are examined one year after the end of the treatment, one finds that the average concentration of acacia in the serum is approximately 0.1 Gm per hundred cubic centimeters. The concentration of acacia in the blood serum of 1 patient, who recently returned for reexamination six years after her last injection of acacia, was 0.01 Gm per hundred cubic centimeters. She had received the average total dose of 90 Gm of acacia.

*Excretion of Acacia in Urine and Stool*—Acacia is not readily metabolized by the animal body and is in part excreted in the urine in a state which has not become so modified as to lose its property of precipitating in the presence of acetone.

The greatest excretion of acacia in the urine of the 3 animals which are the subjects of table 1 and figure 1 occurred in the periods immediately following injections of acacia (fig 1 *b*). In two trial periods, the animals which were given more solution of acacia excreted more. The quantity of acacia excreted is small compared to the amount administered or compared to the concentration of acacia in the serum. The amount of acacia excreted is not proportional to the amount of urine collected in twenty-four hours, for the largest amount of urine sometimes contained the least acacia. Two years following cessation of injections of acacia, traces of acacia still were being excreted in the urine of the 2 living animals.

Certain authors, including Huffman,<sup>6</sup> have reported considerable variation in the amount of acacia which could be recovered from the urine of individual patients. In some cases Huffman was able to recover more than half of the total amount injected intravenously. Hartmann<sup>7</sup> found that acacia appeared in the urine immediately after its intravenous injection and that the

rate of excretion varied with different persons. He also stated that the average excretion was about 25 per cent in the first two days and 60 per cent during the first seven. Moreover, he noticed a maximal concentration of acacia in the urine of 1.3 per cent. Andersch and Gibson<sup>8</sup> found that only small amounts of acacia were eliminated in the urine of animals. They reported that only 20 per cent of the total acacia which was injected intravenously into a patient with nephrosis was recovered in the urine over a period of six weeks, three of the six weeks over which urine was collected followed the last injection. They also reported that the greatest excretion occurred during the period in which the acacia was administered. Butt, Power and Keys<sup>9</sup> reported that about 20 per cent of the total quantity of acacia administered in single or multiple intravenous injections was excreted in the urine in the first eight days after injection and that most of the acacia excreted appeared in the first three days after its administration. Acacia was present in the stool, but in questionable amounts, as the acetone precipitate in normal stool was not determined. Determinations were made at the time the injections of acacia were discontinued.

*Effect on Structure of Liver, Spleen and Kidney*—On gross examination of each of the 3 animals at the time of the first exploration, the day after the last injection of acacia, the liver was estimated to be increased from one fourth to twice normal size. The liver which was most enlarged was that of the animal which received the most acacia, and this liver appeared lighter in color than the livers of the other 2 animals and than the normal livers. The livers of all 3 animals had smooth surfaces and rounded edges, in the latter respect resembling the appearance of a restored liver. They were firmer than normal livers on palpation. Little bleeding occurred from the cut surfaces of the livers of the 2 animals which received the most acacia, the third bled normally. In the abdominal cavity of the animal which had received the most acacia was several hundred cubic centimeters of clear ascitic fluid.

The animals recovered normally from the first exploration. Conditions at the time of the second examination, ten weeks later, were little

6 Huffman, L. D. Solution of Acacia and Sodium Chloride in Hemorrhage and Shock, *J. A. M. A.* **93** 1698-1701 (Nov. 30) 1929.

7 Hartmann, A. F., Senn, M. J. E., Nelson, M. V., and Perley, A. M. The Use of Acacia in the Treatment of Edema, *J. A. M. A.* **100** 251-254 (Jan. 28) 1933.

8 Andersch, M., and Gibson, R. B. Studies on the Effects of Intravenous Injections of Colloids. I. Deposition of Acacia in the Liver and Other Organs and Its Excretion in Urine and Bile, *J. Pharmacol. & Exper. Therap.* **52** 390-407 (Dec.) 1934.

9 Butt, H. R., Power, M. H., and Keys, A. The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, *J. Lab. & Clin. Med.* **24** 690-695 (April) 1939.

changed from those at the time of the first. The livers continued to be enlarged. The surfaces were smooth, and the edges were rounded and not friable. The livers were slightly firmer than normal. They had undergone repair after excision of tissue, as would normal livers. No ascites, however, was found. At the time of the last examination of the 2 living animals, the liver of that 1 of the 2 which had received the more acacia was still slightly, but definitely, enlarged. The edges were still rounded. The liver still was firmer than normal. The liver of that animal of the 2 which had received the less acacia appeared normal.

For comparison, a section was taken for microscopic examination from the liver of a normal animal (fig 2 *a*). Sections of liver taken from the 3 observed animals in the first three months

of sucrose. Hepatic cells were not destroyed, although some polymorphonuclear cells were scattered through the fields.

In the specimen of liver obtained for biopsy after the fourth exploration, the parenchymal cells of the hepatic cords in the midzone of the lobule took the stain about normally, and this zone was distinct (fig 3). It is not possible quantitatively to compare the sections studied at the time that the injections of acacia were discontinued with those obtained two years later, but there continued to be much vacuolation of the parenchymal cells throughout the sections.

Attempts were made to stain these cytoplasmic vacuoles. The vacuoles did not stain for glycogen or for fat. The mucicarmine stain gave a negative result for mucin as did also the congo red stain and the methyl violet stain of frozen sections for

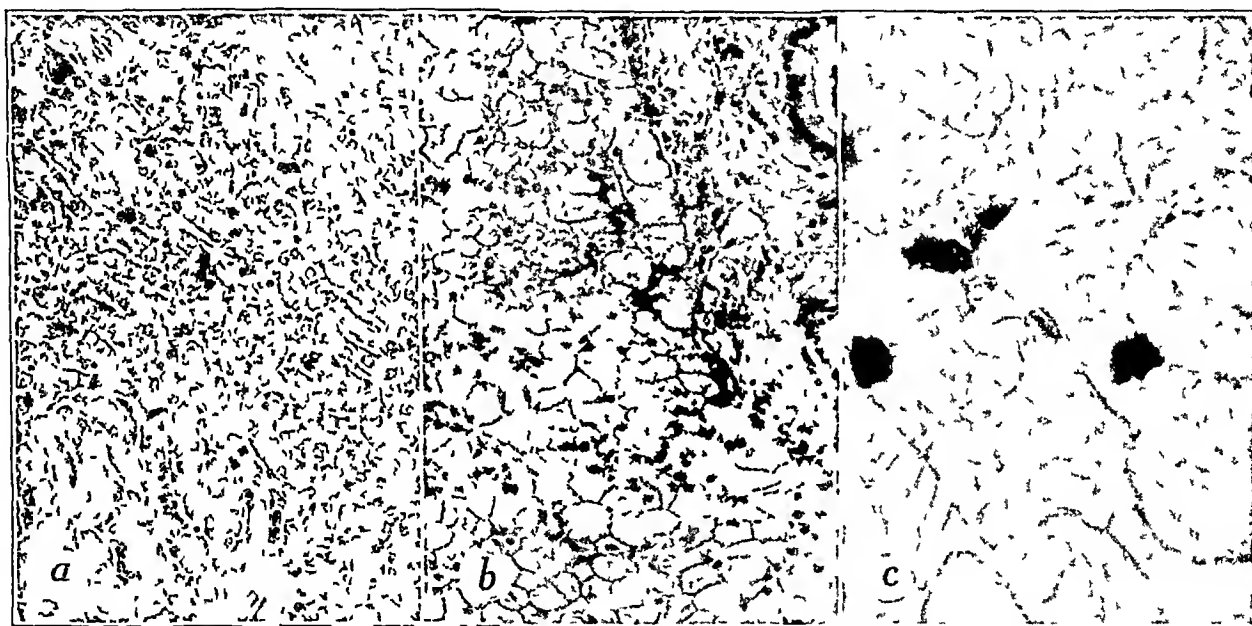


Fig 2—Sections (a) Normal liver of dog ( $\times 160$ ), (b) liver of dog when injections of acacia had just been completed ( $\times 190$ ), (c) same as b under higher magnification ( $\times 960$ )

after discontinuance of the injections of acacia were examined microscopically. Some of the parenchymal cells in the inner zone of the lobule, about the central vein, and in the periportal areas stained more lightly and were clearer than cells of the outer, and especially the midzonal, region of the lobule. The involvement about the central vein resembled the microscopic picture seen in cases of chronic passive congestion of the liver. The central veins were compressed, and the bile ducts were partly obliterated. The parenchymal cells appeared distended, and many of the nuclei were eccentric (figs 2 *b* and *c*). The cytoplasm of the parenchymal cells was vacuolated, so that it had the appearance of hydropic change or of a foam cell, and the picture resembled that of cells seen in renal tubules after intravenous injection

of amyloid. These vacuolated cells may represent stored acacia, but a histologic stain positive for acacia is not available.

The capsule of the spleen and the splenic reticulum also contained relatively large and clearly staining cells, throughout the cytoplasm of which vacuoles were found (fig 4 *a*). The involvement was less pronounced here than in the liver.

The epithelium of both the convoluted and the collecting tubules (fig 4 *b*) of the kidney also contained vacuolated cells. The process was not as diffuse as it was in the spleen and the liver. Vacuolated cells were not seen in the glomerular tufts.

As has been noted earlier, acacia is used in the treatment of chronic glomerulonephritis with re-

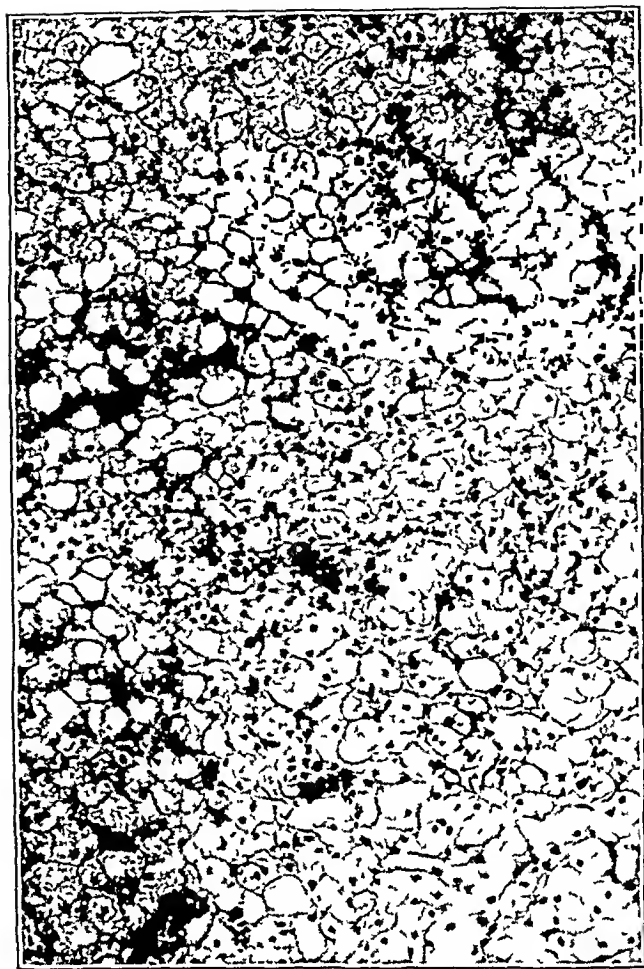


Fig 3—Section of liver of dog two years after injections of acacia had been completed ( $\times 160$ )

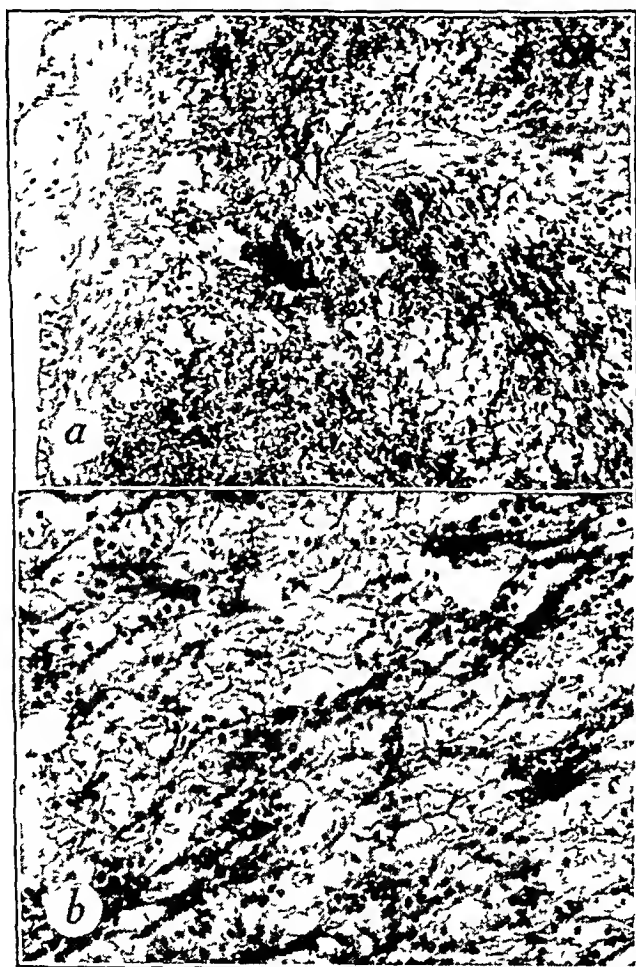


Fig 4—Sections (a) Spleen showing vacuolation in capsule and reticulum ( $\times 120$ ), (b) convoluted tubules of kidney showing vacuolation ( $\times 155$ )

sistant nephrotic edema. Also, it is used in some cases in treatment for acute shock. Hepatic, splenic and renal tissues obtained at necropsy in certain cases of these kinds were examined grossly and microscopically for the presence of the cytoplasmic vacuolation seen in the animal tissues.

In order to establish the significance of the results of examination of tissue of these patients, which presently will be described, it is necessary to record the quantity of acacia administered to them or the concentration of acacia in their blood serums or both at certain periods before their deaths. A woman, 1 of 2 patients with chronic

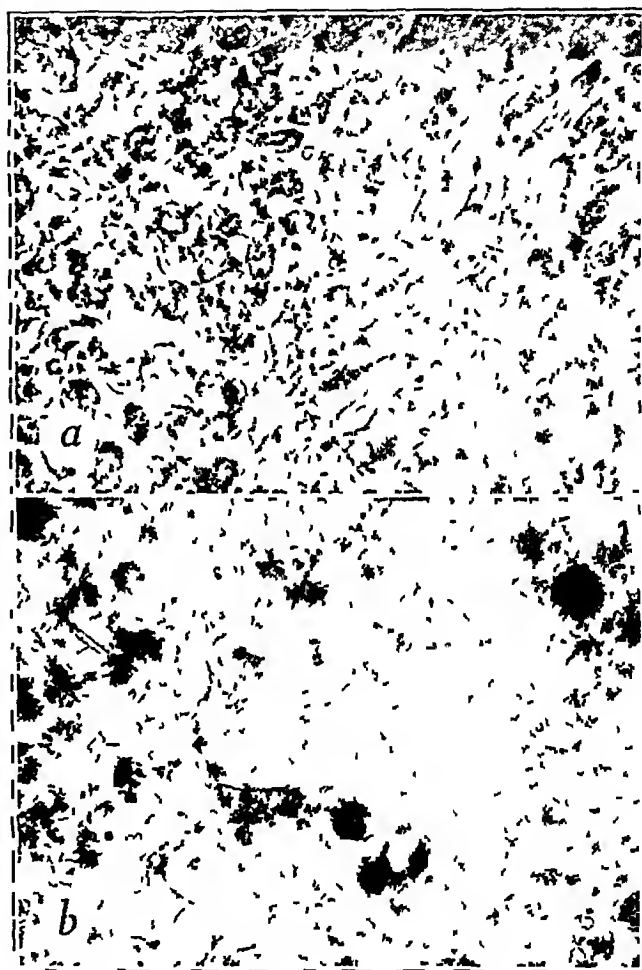


Fig 5—(a) Section of liver of man who had had nephrosis and had received injections of acacia three weeks before death ( $\times 160$ ), (b) darkened areas attributable to positive stain for fat ( $\times 160$ )

glomerulonephritis and nephrotic edema who were treated at the clinic, had received 210 Gm of 6 per cent solution of acacia, which amounted to approximately 37 Gm per kilogram of body weight, and the concentration of acacia in the serum was 17 Gm per hundred cubic centimeters three years before her death. The second patient, a man, whose diagnosis was similar, had received 183 Gm of solution of acacia, or approximately 2 Gm per kilogram of body weight, the concentration of acacia in the serum was 27 Gm per hundred cubic centimeters three

weeks before his death. Other patients had been given acacia for acute shock and had received from 30 to 60 Gm of solution of acacia a few days before death. In all such cases, in spite of the considerable clinical quantities of acacia that had been administered, the livers were approximately of normal size, the surfaces were smooth, and the tissues were of normal consistency. Microscopic sections from these livers did not reveal the inner zonal and periportal lightly and clearly staining areas that were seen in the livers of the animals. The cytoplasm of the parenchymal cells contained fewer large vacuoles, and the stain was positive for fat (fig 5). Acacia may have been present, but its presence was not definitive. The spleen and kidneys appeared normal.

pared for analysis glycogen had largely disappeared as an interfering factor. Qualitative colorimetric estimations with Bial's orcin test for pentoses supported this view.

In the animal that died, approximately 53.6 Gm of acacia was accounted for in the liver, spleen and kidneys, 52 Gm of which was in the liver. The acacia determined to be present in the liver of this animal represented about 18.8 per cent of the total quantity of acacia injected into the animal. Andersch and Gibson have reported that 50 per cent of acacia injected intravenously into rabbits can be accounted for in the liver and about 30 per cent of that injected into dogs.

*Effects on the Blood, Other Than Concentration of Acacia*—In table 2 are recorded the

TABLE 2—Determinations on the Blood During and After Intravenous Injections of Solution of Acacia

Date	Weight, Kg			Protein Fractions												Hematocrit Reading, Cells per 100 Cc		
				Serum Protein, Gm per 100 Cc			Serum Albumin, Gm per 100 Cc			Serum Globulin, Gm per 100 Cc			Fibrinogen, Gm per 100 Cc			Hemoglobin, Gm per 100 Cc		
	Animal			Animal			Animal			Animal			Animal			Animal		
	9	7	8	9	7	8	9	7	8	9	7	8	9	7	8	9	7	8
1/7/42	64	70	58															
1/15/42	64	70	60	48	33	30											52.0	42.0
1/21/42	64	74	58	50	32	32											52.0	40.0
2/5/42	70	74	58	57	41	34											53.0	34.0
2/19/42	70	72	55	49	38	32	30	20	17	18	18	15	0.27	0.16	0.23	15.3	12.4	4.2
3/3/42	72	72	54	50	39	27	32	19	15	19	19	12	0.43	0.39	0.32	17.1	12.4	7.9
3/19/42*	72	72	54	49	35	30	29	22	23	20	13	0.7	0.30	0.24	0.25	16.0	12.0	6.8
4/16/42	74	72	52	56	48	38	34	26	22	22	22	17	0.32	0.42	0.53	16.8	12.2	10.0
4/30/42	78	72	48	57	54	46	37	29	28	20	25	19	0.46	0.34	0.46	17.9	14.6	9.5
5/29/42	56	74	56	55	52	53	34	26	31	21	26	22	0.53	0.48	0.76	15.2	12.0	11.4
9/8/42	66	66		61	47		37	32		24	15		0.41	0.43		8.5	7.4	
11/30/42	68	64		59	49		28	18		31	31		0.61			12.0	15.2	
2/4/43	68	66		61	55		35	30		26	26		0.52	0.46		16.1	15.3	
4/21/43				58	51		36	30		22	21		0.27	0.23				
3/23/44	66	72		61	53		37	34		24	19		0.47	1.00		16.0	16.0	

\* Acacia was not injected after 3/23/42.

*Chemical Determinations of Acacia in the Liver, Spleen and Kidneys*—By chemical analysis, it appears that acacia is deposited in the liver, the spleen and the kidneys in that order in diminishing quantities. At the time when the first abdominal explorations were made and when the injections of acacia had been discontinued, the concentration of acacia in the serum was highest and acacia was being stored in the liver. Approximately ten weeks later, when the second abdominal explorations were made, the concentrations of acacia in the serum were decreasing, and storage of acacia in the livers of all animals appeared to be increased. The hepatic tissues analyzed at the time of the last exploration contained less acacia than at any other of the four periods, and the concentration of acacia in the serum was lowest. The data obtained indicated that by the time samples of tissue had been pre-

pared for analysis glycogen had largely disappeared as an interfering factor. Many workers have noted decrease in the total protein, affecting both the albumin and the globulin fractions, following intravenous injection of solution of acacia. Dick and associates<sup>10</sup> noted that the concentration of total proteins of dogs which had been given injections of acacia was decreased but that the concentration returned to normal after administration had been discontinued. Heckel and associates<sup>11</sup> suggested two mechanisms for this diminution: (1) that the hepatic cells, engorged with acacia, are not able to produce the necessary

10. Dick, M. W., Warweg, E., and Andersch, M. Acacia in the Treatment of Nephrosis, *J. A. M. A.* **105**: 654-657 (Aug. 31) 1935.

11. Heckel, G. P., Erickson, C. C., Yuile, C. L., and Knutti, R. E. Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia, *J. Exper. Med.* **67**: 345-360 (March) 1938.

amount of plasma protein and (2) that the plasma protein is removed from the blood stream in an attempt to return plasma volume and colloidal osmotic pressure to normal limits. Yuile and Knutti<sup>12</sup> observed that the plasma volume is increased after injections of acacia and that while this increase obtains the concentration of total protein is low. Goudsmit and co-workers<sup>13</sup> reported that most of the decreases in concentration of total protein were due entirely to dilution. We do not have enough information definitely to explain the decrease in concentration of total protein. It may be a dilution effect to compensate for circulating serum acacia. However, we do not believe that it is caused by, but rather that it accompanies, the administration of acacia, that is the function of the hepatic cells is not seriously disturbed. Also, as has been reported, some others of the functions of the hepatic cells are not disturbed by the presence of acacia.<sup>14</sup>

In a series of determinations made on normal animals, we have found the normal concentration of total proteins to range between 6.5 and 7 Gm per hundred cubic centimeters of serum. The concentration of total proteins was decreased similarly in the blood of the 3 observed animals. The degree of decrease was proportional to the amount of solution of acacia given. In the blood of the 2 animals given the larger amounts of solution of acacia, the concentration of total protein was lowered to a greater degree than it was in the blood of the animal which received the smaller amount of solution of acacia. Also, this decrease was greater in the animal which received the most solution of acacia than it was in the animal which received the next to the largest amount. The decreases noted occurred practically at the beginning of the period of administration of acacia, and the values maintained themselves or tended to improve in spite of continued injections over the remaining portion of the period of seventy-six days of administration. The normal plasma albumin fraction is about 4 Gm and the globulin fraction, about 3.5 Gm, per hundred cubic centimeters, the ratio is slightly greater than 1.1. In comparison with these normal values, it is suggested that the albumin was decreased more than the globulin and that also the ratio was reduced below that of normal animals,

the ratio, however, was not inverted. Edema did not develop in 2 of the observed animals, in 1 of which the concentration of total protein was depressed below 4 Gm per hundred cubic centimeters. The animal which received the most acacia, and the value for total protein of which was lowest, had ascites at the time when the injections of acacia were discontinued and when the first exploratory operation was performed. Also, there was slight edema of the hindlegs at that time. At no time was generalized edema present. In spite of the high concentration of acacia in the serum and the low value for total proteins, the dogs that were still living at the time this paper was written appeared alert and well, as has been said.

The total plasma proteins and also the albumin and globulin fractions began to increase almost at once after the injections of solution of acacia had been discontinued. In one month, the concentration of total proteins in the blood of all 3 observed animals increased from 0.7 to 1.3 Gm per hundred cubic centimeters. This indicates that the serum proteins could be restored. The return was slow but steady, the values were not within the normal range at the end of the period of observation.

The ultimate recovery of a patient with hypoproteinemia is dependent on his ability to restore to normal the concentration of total proteins. Clinically, we have observed many patients with chronic glomerulonephritis and the nephrotic syndrome the concentration of whose total proteins has increased from below 4 Gm per hundred cubic centimeters to normal—that is, from 3.6 to 6.2 and from 4 to 7.5 Gm, per hundred cubic centimeters—after therapeutic administration of acacia. This increase has taken place in eleven to eighteen months following treatment. One of these patients, aged 35 years, had been known to have renal disease for four years when first treated at the clinic. At the time of a recent follow-up inquiry, this patient stated that he felt well and was working full time daily. This is the evidence on which we base the belief that the temporary decrease in the concentration of total protein accompanies, but is not caused by, the administration of acacia.

Under the conditions of this study the fibrinogen was never depressed to the low limits reached in the work of Heckel and his associates and of Yuile and Knutti. The values for fibrinogen fluctuated, but not directly with the decrease in the total proteins nor with the decrease in the fractions of albumin and globulin. These determinations did not vary directly with the quantity of solution of acacia administered. Also, the

12 Yuile, C. L., and Knutti, R. E. Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia, *J. Exper. Med.* **70** 605-613 (Dec.) 1939.

13 Goudsmit, A., Jr., Binger, M. W., and Power, M. H. Acacia in the Treatment of the Nephrotic Syndrome, *Arch. Int. Med.* **68** 701-712 (Oct.) 1941.

14 Metcalf, R. G., and Hawkins, W. B. Plasma Protein, Bile Salt and Cholesterol Metabolism as Influenced by Multiple Injections of Gum Acacia in Bile Fistula Dogs, *Am. J. Path.* **15** 429-444 (July) 1939.

values for fibrinogen did not remain low during the period of administration of solution of acacia. One determination of plasma fibrinogen made on animal 7, which received the second largest amount of solution of acacia, reached 1 Gm, this indicated that the source of supply of this protein fraction, which many workers feel is mainly the liver,<sup>15</sup> was able to sustain an increase of values for fibrinogen to above normal. If the plasma fibrinogen is used as a means of estimating the relative degree of hepatic function, according to these determinations the hepatic cells of the observed animals were not seriously injured. Other authors have reported that in determining concentration of fibrinogen they found the time necessary for the clot to form to be from twenty minutes to one hour. To determine whether precipitation time might be a factor in obtaining all the fibrinogen present in plasma that contained acacia, this process was controlled at twenty minutes, at one hour and overnight. The determinations of fibrinogen made at these different times on the different specimens of plasma were nearly alike.

The animal which received the largest dose of solution of acacia had a normal value for prothrombin during the middle part of the course of injections of acacia. Duplicate determinations on all 3 observed animals, sixty-nine days after the injections of acacia had been begun, also gave normal results. The coagulation time always was normal, between five and ten minutes. Clot retraction appeared normal. Bleeding time was normal.

The sulfobromophthalein sodium test of hepatic function was made fifty days after the injections of acacia had been begun, and it was found that less than 5 per cent of dye was retained by any of the 3 observed animals. These results were interpreted as being normal.

The concentration of hemoglobin also fluctuated, increasing slightly between injections,

<sup>15</sup> Foster, D. P., and Whipple, G. H. Blood Fibrin Studies. IV. Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula, Notes Concerning the Origin of Fibrinogen in the Body, *Am J Physiol* 58:407-431 (Jan 1) 1922.  
<sup>16</sup> Berryman, G. H., Bollman, J. L., and Mann, F. C. The Influence of the Liver on the Proteins of the Blood Plasma, *ibid* 139:556-562 (Aug) 1943.

and, with reference to the 2 living animals, at the time of writing of this paper these values had returned to normal. Hematocrit values decreased after injections of solution of acacia and increased between injections. They became normal and continued so when the injections were discontinued (table 2). Macrocytic anemia has been observed repeatedly among patients whose hepatic substance has undergone varying degrees of damage and destruction.<sup>16</sup> The changes in the blood are variable, and anemia does not develop in all cases in which the liver has sustained damage. Blood smears taken in the early days of administration of acacia and throughout the period of observation, including the day on which administration was discontinued and two years following discontinuance of administration, were examined for evidence of macrocytosis. At all times the mean diameters of the cells were within the ranges determined on normal dogs, 6.5 to 7.2 microns.

There was definite increase in the sedimentation rate of the animals which received acacia as contrasted with that of normal dogs. The greatest increase was that of the animal which received the largest amount of acacia, and the least increase occurred in the animal which received the smallest amount of acacia.

#### SUMMARY

In a period of seventy-six days 3 dogs received eight, twenty-two and twenty-six times the amount of acacia usually given therapeutically to patients. The animal that received the largest amount died four months after discontinuation of the injections of acacia. No evidence of profound functional hepatic injury was found, although large amounts of acacia were present in the liver. In the livers of the other 2 dogs acacia was present twenty-six months after the last injection of acacia. These animals survived four exploratory laparotomies with biopsy of the liver and remained in good condition. These results do not contraindicate the use of acacia therapeutically under careful management.

<sup>16</sup> Kracke, R. R., and Garver, H. E. Diseases of the Blood and Atlas of Hematology, Philadelphia, J. B. Lippincott Company, 1937, p. 249.

# HABITUS OF PATIENTS WITH ACTIVE SICKLE CELL ANEMIA OF LONG DURATION

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NEW ORLEANS

In many disease states the general physical characteristics of the patient aid the examiner in making an etiologic diagnosis. In acromegaly, cretinism or myxedema, achondroplasia, pituitary basophilism, mongolism, adiposogenital dystrophy, rickets and many other conditions valuable information can be obtained by observation of the nude subject. Patients with long-standing active sickle cell anemia have a fairly characteristic habitus<sup>1</sup> which may be considered typical of the disease. In several instances the diagnosis of sickle cell anemia was suspected on inspection of the nude subject by physicians familiar with the sickle cell anemia type of habitus. In these instances subsequent hanging drop preparations showing sickling and positive diagnostic parameters<sup>2</sup> indicated the correctness of these observations.

The purpose of this paper is to point out the characteristics of the habitus of patients with sickle cell anemia of long duration and to discuss some of the factors which contribute to its production.

Fifteen patients between the ages of 6 and 32 years with active sickle cell anemia and 4 patients between the ages of 30 and 47 years with sickle cell anemia (the sickling phenomenon without anemia or other manifestations of the disease) were chosen for study. All patients with sickle cell anemia had sickling of the erythrocytes and positive diagnostic parameters. Reports on detailed anthropometric studies on these patients have been published elsewhere<sup>1</sup>. All patients were Negroes, and most of those with sickle cell anemia had been hospitalized and observed repeatedly during exacerbations of their disease. The majority of the patients had associated heart disease, which probably resulted from their long-standing anemia<sup>3</sup>. The adult and adolescent male patients had the most numerous hospital admissions, and as a group represented the most severely diseased patients. For each patient with sickle cell anemia, 10

control subjects of the same sex, age and color were chosen for comparison.

Two methods of study were utilized: (1) The general appearance of the subjects was evaluated by direct observation and from photographic prints, and (2)

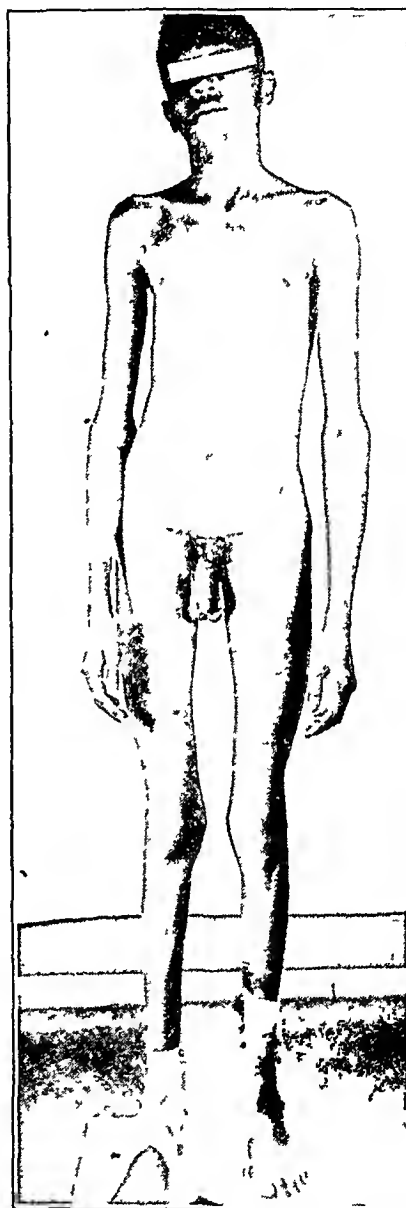


Fig 1—This 19 year old patient has had approximately 2,000,000 erythrocytes for at least the past three years. There is no evidence of cardiac disease. He illustrates the linear type of habitus and a definite loss in weight. The legs are long and the trunk relatively short.

anthropometric measurements were obtained by means of standard anthropometric technique and equipment<sup>4</sup>. Of

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1 Winsor, T, and Burch, G E. The Habitus of Patients with Sickle Cell Anemia, *Human Biol* **16** 99-113 (May) 1944.

2 Winsor, T, and Burch, G E. Diagnostic Physicochemical Blood Tests in Sickle Cell Anemia, *Am J M Sc* **207** 152-160 (Feb) 1944, A Study of the Sedimentation Rate of Erythrocytes in Sickle Cell Anemia, *Arch Int Med* **73** 41-52 (Jan) 1944.

3 Winsor, T, and Burch, G E. Electrocardiogram and Cardiac State in Patients with Sickle Cell Anemia, to be published.

4 Hrdlička, A. *Practical Anthropometry*, Philadelphia, Wistar Institute of Anatomy and Biology, 1939.

these two methods the former yielded valuable information which could not be adequately recorded by direct measurement. The latter gave significant information regarding in particular the skeletal structure.

#### THE HABITUS

*Clinical Appearance*—The habitus of patients with active sickle cell anemia was often striking and at times characteristic, particularly of patients in whom the disease had been active for many years.



Fig 2—The legs are long and the trunk short. The anteroposterior diameter of the chest is increased as compared with the lateral diameter. The neck appears short. There is a definite kyphosis in the upper region of the thorax. The normal lower lumbar lordotic curvature is increased. The patient has complained of intermittent backache for the past four years. Roentgenographic changes in the bodies of the lumbar vertebrae are shown in figure 5.

The following characteristics were observed in the adult patients and are exemplified in figures 1 and 2.

The patients were slender and appeared relatively tall, although they were not necessarily of greater than average height. The shoulders and

hips were narrow, producing a linear type of habitus (fig 1). Occasionally the head was somewhat abnormal in shape (dolichocephalic, scaphocephalic or otherwise unusual). The neck appeared short. The normal upper dorsal kyphotic curvature was definitely accentuated (fig 2), and the lower lumbar curvature was excessively lordotic. The arms and legs were thin and long and the trunk short (figs 1 and 2). The chest was deep and narrow, producing a "hoop-chested" appearance. The hands, fingers, feet and toes were long and narrow. The hands have been well termed "spider hands" (fig 3). Signs of hypogonadism (such as genital hypoplasia or atrophy, hypotrichosis and high-pitched voice) were occasionally encountered.

The appearance of the children was either slightly or strongly abnormal, depending on the



Fig 3—"Spider fingers" with generalized decalcification in a 17 year old girl who has had severe chronic active sickle cell anemia for at least eight years. Osseous changes are present elsewhere in the body.

severity and duration of the disease. In this group the thin arms and legs, the "hoop chest" and the protruding abdomen were the most outstanding characteristics (fig 4). Any of the characteristics just described for the adult patients might be present, however.

In subjects with sickle cell anemia no characteristic features were seen.

*Roentgenographic Manifestations*—Although the roentgenographic observations were not constant, certain features should be mentioned. Changes in the skull were rarely present and consisted of decalcification with exaggeration of the normal reticulations, best seen in the region of the vertex. Only 1 of 8 patients for whom roentgenograms of the skull were taken showed the typical "hairbrush" appearance. The vertebral bodies sometimes showed pronounced de-

calcification and sometimes showed crescentic depressions of their superior and inferior borders (fig 5). These changes were most noticeable in the lumbar region. The hands showed "spider fingers," with pronounced decalcification



Fig 4—This 7 year old patient demonstrates the deep chest, "hoop chest," and the protuberant abdomen. The spleen and liver were not palpable, and the abdomen was tympanitic. There has been no appreciable change in the degree of abdominal protuberance during the past three years.

of the metacarpal bones and phalanges (fig 3) in some

*Anthropometric Measurements*—The mean, maximum and minimum measurements are listed in the table. All measurements were made according to the metric system, and the indexes are expressed in per cents. The average values for the patients with sickle cell anemia represent the averages for 3 male patients, the ages being 21, 24 and 30 years. The control groups consisted of 10 subjects each of the same sex, age and color, making a total of 30 control subjects.

The following points are emphasized in the table. The mean stature of the diseased subjects was slightly less than that of the controls. The mean weight of the patients with sickle cell anemia was noticeably less than that of controls (table b). Although both stature and weight were reduced, the weight was reduced more than the stature (table c). The span, like the stature, was less for the patients than for the controls, however, the relation of the span to the stature was not significantly different in the two groups (table d). The sitting height as compared to the stature was shorter in the diseased group than in the controls (table e). The average sitting height of patients with sickle cell anemia was 47.2 per cent of the stature, and of the control subjects it was 51.5 per cent. The average pubic height (measured from the floor to the superior portion of the symphysis pubis) was 55.9 per cent of the stature in the diseased group and 53.3 per cent in the control group. The average widths of the shoulders and pelvis were less in the diseased group than in the controls (table f and g). The pelvic width in the diseased



Fig 5—Changes in the vertebral bodies seen in the patient illustrated in figure 2. There is generalized decalcification with crescentic depressions of their superior and inferior aspects. The changes are most conspicuous in the fifth lumbar vertebra.

group was narrow in relation to the stature, being 14.6 per cent of the stature as compared with

15.9 per cent in the controls (table *h*) The circumferences both of the chest and of the abdomen were less for the patients than for the controls (table *i* and *j*) The average abdominal circumference in the diseased group was relatively large, averaging 87.3 per cent of the thoracic circumference in the diseased patients and 83.5 per cent in the controls The anteroposterior diameter of the chest averaged 77.5 per cent of the lateral diameter in the diseased group and 67.1 per cent in the controls Items *m* and *n* in the table illustrate the long narrow character of the hand and foot The circumference of the leg was decidedly reduced (table *o*) There was a tendency to dolichocephaly (table *p*)

Figures 6 and 7 show a few of the characteristics which constituted the drepanocytic habit-

Mean Anthropometric Measurements for Three Patients with Sickle Cell Anemia and for Thirty Normal Subjects

Measurement or Index	Patients with Sickle Cell Anemia, Mean (Extremes) Cm, % or Kg	Controls, Mean (Extremes) Cm, % or Kg
(a) Stature	168.2 (171.0-165.5)*	171.8 (177.0-160.3)
(b) Weight	43.0 (45.0-41.0)	61.0 (79.5-51.2)
(c) Weight/stature	25.6 (26.3-24.8)	35.5 (41.8-41.9)
(d) Span/stature	105.9 (106.0-105.8)	106.2 (107.6-105.4)
(e) Sitting height/stature	47.2 (47.5-46.9)	51.5 (51.6-51.4)
(f) Shoulder width	36.5 (38.8-34.3)	41.0 (44.6-37.3)
(g) Pelvic width (intercrural)	24.6 (24.7-24.6)	27.4 (30.0-25.6)
(h) Pelvic width/stature	14.6 (14.9-14.4)	15.9 (16.9-15.0)
(i) Circumference of chest	72.5 (75.0-71.1)	86.3 (97.3-78.8)
(j) Abdominal circumference	63.3 (63.6-63.0)	72.1 (86.5-68.1)
(k) Anteroposterior diameter of chest	18.6 (19.0-18.2)	19.0 (21.9-17.2)
(l) Lateral diameter of chest	24.0 (26.0-22.0)	28.3 (31.7-24.4)
(m) Hand breadth/length	41.7 (43.1-40.8)	45.2 (45.6-44.1)
(n) Foot breadth/length	36.7 (37.0-34.2)	38.0 (41.3-37.2)
(o) Circumference of calf	22.1 (25.4-21.8)	32.5 (36.6-30.5)
(p) Head width/length	70.5 (72.7-68.2)	77.1 (78.5-76.1)

\* Maximum and minimum values are shown within the parentheses

tus in 7 children, 2 adolescents and 6 adults These graphs illustrate the changes in body configuration which were observed at different age levels and may suggest changes which take place as growth and the disease processes progress For each patient with sickle cell anemia, 10 normal subjects of the same sex, age and color were studied as controls, making a total of 70 children, 20 adolescents and 60 adults, or 150 control subjects in all In the older age groups the patients were more linear in build than the controls (fig 6) The circumference of the legs was considerably less than that of the legs of the controls at all age levels, and the difference was greatest in the adolescents and adults The body weight was less than that of the controls This difference also was greatest in the adults and adolescents The hands were consistently

longer and narrower than the hands of controls at all age levels (fig 6) The sitting height was less than that of the controls in all three groups (fig 7) The legs, from youth to adulthood, were somewhat longer than those of the

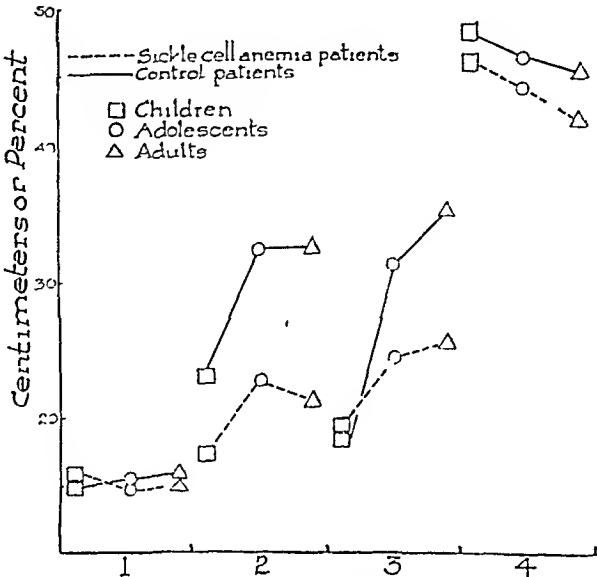


Fig 6—Changes in body configuration seen at three different age levels, during childhood, adolescence and adulthood The figures represent the averages of 15 patients with sickle cell anemia and of 150 normal subjects used as controls The numbers at the base of the graph represent the following comparisons (1) width of the pelvis as compared with the stature in per cents, (2) circumference of the leg in centimeters, (3) body weight in relation to the stature in per cents, and (4) width of the hand in relation to the length in per cents

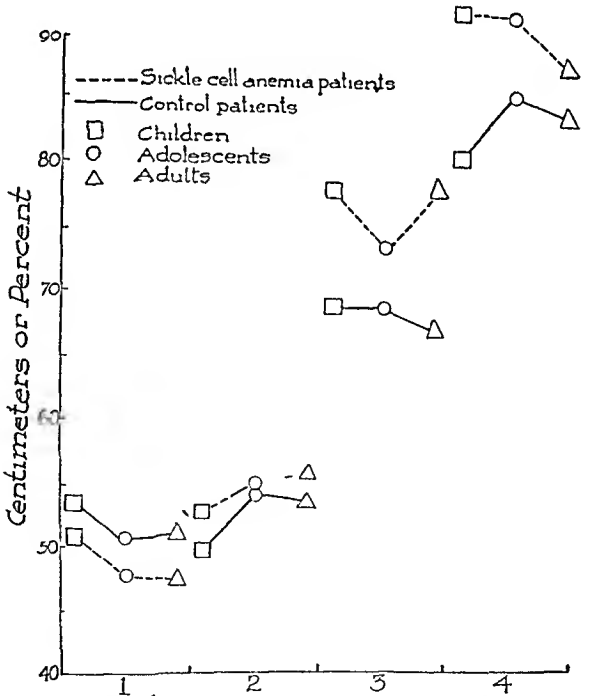


Fig 7—Other comparisons from the same patients described in figure 6 (all comparisons expressed in per cents) (1) sitting height in relation to the stature, (2) pubic height in relation to the stature, (3) depth of the chest in relation to the width, and (4) abdominal circumference in relation to thoracic circumference

controls The chest had a "hoop-chested" appearance in the three age groups In the older age groups, the abdominal girth in relation to the thoracic girth was less than that of the controls (fig 7)

Although in isolated instances the change in body form with increasing age was not distinctive, there was often a major difference between the body features existing in childhood and those seen in adulthood

#### COMMENT

It is not surprising that the habitus is abnormal in patients with long-standing active sickle cell anemia, as practically all tissues of the body are affected by the disease processes The organs involved are so numerous and the signs and symptoms so protean that Wintrobe has labeled this disease, in contrast to syphilis, the "little imitator"<sup>5</sup> The cardiovascular system is affected in about 90 per cent of patients, and a diagnosis of rheumatic or congenital heart disease was erroneously made for more than half the patients at Charity Hospital<sup>3</sup> Involvement of the nervous system has produced paralytic changes, for which leg casts have been applied under the mistaken diagnosis of poliomyelitis Pulmonary infarcts have been repeatedly and mistakenly diagnosed as bacterial or atypical pneumonia, and treatment for the former with sulfonamide drugs has produced definite injury to the kidneys, which were already injured by the disease process itself The abdominal viscera, the spleen, liver and gastrointestinal tract, are all frequently involved, and erroneous pre-operative diagnoses of ruptured peptic ulcer, ruptured gallbladder or acute appendicitis have led to unwarranted surgical intervention among these patients, in whom there is a high surgical mortality In addition to the involvement of the aforementioned organs and organic systems, diseases of the endocrine, hemopoietic, vascular and osseous systems serve to produce changes in the body type With involvement of so many organ systems, it is not surprising that the habitus of these patients is altered

The anemia itself is probably of great importance in altering the habitus, as patients with sicklemia do not have an abnormal habitus<sup>1</sup> Severe anemia produces poor nutrition to all organs and tissues, and the tissues most sensitive to anoxia will be affected to the greatest degree If, as a result of anoxia, the gonads became atrophic and the pituitary remained active, a hypogonad type of habitus would result The

subject would be tall, the span would exceed the stature, and the bone age would be considerably retarded If the gonads remained functioning normally and the pituitary activity was depressed, the subject would be of decreased stature, the span to stature ratio would not be abnormal, and there would be no noticeable retardation of the bone age In most of the patients with sickle cell anemia described in this study, the stature was decreased, and in some there was also evidence of hypogonadism Thus it is possible that both the gonadal and the pituitary activities were decreased to produce this picture

At just what age characteristic features of the habitus manifest themselves depends to a great extent on the severity of the disease and on the age at which the illness becomes active It is conceivable that the typical habitus might be present at or before birth if severe intrauterine sickle cell anemia were present Definite deviations from the normal have been repeatedly recognized during the first decade of life of such patients

The development of the sickle cell anemia habitus may be likened to the development of the habitus in patients with acromegaly When the disease is far advanced and of long duration, the clinical picture is easily recognized When the disease process is slight or when full physical development has not taken place, as in younger persons, the typical configuration is often not apparent Also, like that of patients with acromegaly, the body type in sickle cell anemia is not due to genetic characteristics, as is sometimes true of patients, for example, with achondroplasia, but is a result of the disease processes themselves The sickle cell anemia habitus is unlike the "peptic ulcer habitus" or the "poliomyelitis physiognomy" In these the habitus is said to be genetic in origin and allegedly indicates a "constitutional" predisposition to the disease

The essential features of the sickle cell anemia habitus are as follows

The adults have linear builds, emaciation, long legs, "hoop chests," short trunks, "spider hands," lumbar lordosis and upper dorsal kyphosis, tendencies to hypogonadism and general appearance of fragility The children have "hoop chests," enlarged, protruding abdomens and thin legs Changes encountered in adults may be present in children if the disease is severe

At this point it is wise to draw attention to a few physical characteristics of normal American Negroes as compared with those of white Americans, as a knowledge of these physical traits helps to prevent confusion resulting from normal

<sup>5</sup> Diggs, L W, Pulliam, H N, and King, J C The Bone Changes in Sickle Cell Anemia, South M J 30 249-259 (March) 1937

racial differences.<sup>6</sup> The adult Negro is allegedly shorter in stature and lighter in weight than the white adult. This may not be true of Negroes from all localities. They are more linear in habitus, and the head tends to dolichocephaly. The trunk is relatively short, and the pelvis is flat and narrow. The length of the hands and feet is great as compared with their widths. The arms and legs are long, and the span exceeds the stature by as much as 12 cm in some Negro men. There is an increase in the curvature of the lumbar portion of the spine, which produces a relative lumbar lordosis. The physical characteristics of the normal Negro may be found elsewhere.<sup>7</sup> In sickle cell anemia these normal characteristics are often exaggerated.

The habitus of patients with sickle cell anemia superficially resembles that encountered in patients with primary hypogonadism. There are certain variations, however, which aid in differentiating these two conditions. In patients with sickle cell anemia the span does not tend to exceed 107 per cent of the stature. In primary hypogonadism the span may exceed 112 per cent of stature or more. In sickle cell anemia the stature is often less than normal, while in primary hypogonadism it is greater than normal. In sickle cell anemia "spider hands" are present. The fingers are long and thin, and there is roentgenologic evidence of decalcification of the metacarpals and phalanges. Localized areas of periostitis may be seen. The body weight in primary hypogonadism is not usually abnormally decreased, while in active sickle cell anemia it is usually sharply reduced. In both disease states the trunk is short as compared with the stature. In primary hypogonadism the decrease in the

sitting height is due to definite overgrowth of the long bones of the legs, while in sickle cell anemia it is due for the most part to shortening of the trunk as a result of a decrease in the height of the lumbar vertebrae.<sup>8</sup> Unusual degrees of kyphosis and lordosis due to changes in the bodies of the vertebrae (fig 3), enlargement of the abdomen, enlargement of the anteroposterior diameter of the chest ("hoop chest") and decreased circumference of the legs tend further to differentiate these two conditions.

In sickle cell anemia some of the adult patients with severe anemia have evidence of gonadal hypofunction. In men, the scanty facial, thoracic and pubic hair, the testicular atrophy and the high voice are striking features which are occasionally seen. Retarded bone age is present in some adult patients.<sup>9</sup> This was not encountered by us, however. The slight increase in length of the lower extremities over that seen in normal persons may be evidence of some degree of hypogonadism. This hypogonadism, when present, is a secondary and not a primary type.

Changes in the external and roentgenologic appearance of the bones of the skull have been discussed by others.<sup>8</sup> Scaphocephaly with roentgenologic evidence of thickening of the outer table of the vertex,<sup>9</sup> dolichocephaly<sup>10</sup> and macrocephaly<sup>11</sup> have all been described. Diggs, Pulliam and King<sup>8</sup> have pointed out that up to 1937 there were only 9 patients described in the literature in whom typical changes of the skull were present. In their series of patients, only 1 had significant osseous changes in the skull. The rarity of these changes should be appreciated. Of the 15 Charity Hospital patients in this series, only 2 had definite gross abnormalities in the shape of the skull. Of the 8 patients in whom the skull was studied roentgenographically, only 1 showed the "hairbrush" appearance with thickening of the outer table. It is felt that the so-called typical roentgenographic changes in the skull are both uncommon and nonspecific, as

6 Herskovits, M. J., Cameron, U. K., and Smith, H. The Physical Form of Mississippi Negroes, *Am J Phys Anthropol* **16** 193-201 (Oct-Dec) 1931. Hrdlička, A. The Full-Blooded American Negro, *ibid* **12** 15-33 (July-Sept) 1928. Herskovits, M. J. Anthropometry of the American Negro, New York: Columbia University Press, 1930. Hrdlička, A. Anthropology of the American Negro, *Am J Phys Anthropol* **10** 205-235 (April-June) 1927. Royster, L. T., and Hulvey, C. N. Relations of Weight, Height, and Age in Negro Children, *Am J Dis Child* **38** 1222-1230 (Dec) 1929.

7 Royster, L. T. Body Types of Negro Children, *Arch Pediat* **53** 259-266 (April) 1936, *Tr Sect Pediat*, A. M. A., 1935, pp 133-139. Beckham, A. S. A Study of Weight and Stature of Negro City Children of Adolescent Age, *Human Biol* **10** 124-139 (Feb) 1938. Herskovits, M. J. Physical Types of West African Negroes, *ibid* **9** 483-497 (Dec) 1937. Mustard, H. S., and Waring, J. I. Height and Weights of Colored School Children, *Am J Pub Health* **16** 1017-1022 (Oct) 1926. Todd, T. W., and Lindala, A. Dimensions of Body, *Am J Phys Anthropol* **12** 35-119 (July-Sept) 1928.

8 Vogt, E. C., and Diamond, L. K. Congenital Anemias Roentgenologically Considered, *Am J Roentgenol* **23** 625-640 (June) 1930. Moore, S. Bone Changes in Sickle Cell Anemia, *J Missouri M A* **26** 561-564 (Nov) 1929. Feingold, B. F., and Case, J. T. Roentgenographic Skull Changes in Anemias of Childhood, *Am J Roentgenol* **29** 194-202 (Feb) 1933.

9 Harden, A. S., Jr. Sickle Cell Anemia Changes in the Vessels and in the Bones, *Am J Dis Child* **54** 1045-1051 (Nov) 1937.

10 Rose, C. B. Some Unusual X-Ray Findings in Skulls, *Radiology* **13** 508-514 (Dec) 1929.

11 Grinnan, A. G. Roentgenologic Bone Changes in Sickle Cell and Erythroblastic Anemia, *Am J Roentgenol* **34** 297-309 (Sept) 1935.

the changes cited are encountered in other clinical states, such as Cooley's anemia and congenital hemolytic icterus<sup>12</sup>

It may be said that the habitus in patients with sickle cell anemia is a changing one and striking variations in the physical characteristics are to be expected. The dynamic character of the disease tends to mold and remold the body type as the extent and duration of the disease vary. Many patients with mild disease or with disease of short duration will not exhibit the habitus just described.

Sickle cell anemia presents a difficult problem in diagnosis, only because it is forgotten when a differential diagnosis is under consideration. One significant advantage of a knowledge of the habitus in active sickle cell anemia is that on inspection of the patient one is immediately reminded of the disease entity and thus has the disease in mind before considering its diagnosis.

#### SUMMARY

The habitus of 15 patients with sickle cell anemia and of 4 with sickle cell trait was studied.

The body type of patients with sickle cell anemia was variable in its manifestations because of the dynamic character of the disease. The presence of the sickle cell anemia habitus depends

on the extent and duration of the disease processes and on the age of the patient at the time of onset. A characteristic habitus was not encountered in patients with sickle cell trait. The syndrome was most characteristic in adults and may be described as follows. The habitus was linear, the subjects were underweight, the hips and shoulders were narrow, and the stature was decreased. There was an increased upper dorsal kyphosis and lumbar lordosis and an increase in the anteroposterior diameter of the chest ("hoop chest"). The trunk was short and often showed roentgenologic evidence of flattening of the lumbar vertebrae. The arms and legs were long, but the relationship between the span and the stature was not abnormal for Negroes. The hands ("spider hands") and feet were long and narrow, and there was roentgenologic evidence of decalcification of the metacarpals and phalanges.

The external genitalia were occasionally atrophic, and facial hair was sometimes scanty.

In the children, many of the changes just mentioned were slight, the more constant observations being the "hoop chest," the large abdomen and the small circumference of the legs.

The factors which seem to contribute to the sickle cell anemia habitus are the anemia, the cardiovascular disease, the endocrine changes and the changes in the osseous system.

<sup>12</sup> Williams, H. U. Human Paleopathology, Arch. Path. 7:839-902 (May) 1929. Diggs, Pulliam and King.<sup>5</sup>

# CIRCULATION IN ACUTE MYOCARDIAL INFARCTION

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Myocardial infarction as a clinical entity differs in many respects from other forms of heart disease. In most other conditions leading to cardiac strain and insufficiency the abnormal process affects the heart slowly and gradually, allowing some time for adjustment and adaptation. In infarction the lesion in the myocardium develops suddenly, resulting in partial necrosis of it, and in surviving patients the remaining healthy muscle takes over the function of the whole unit instantaneously. The derangement of the circulation resulting from this sudden insult to the heart is well suited for clinical study, because the exact time of its onset is usually clinically evident. The clinical picture of myocardial infarction is well known. A great deal of work has been done on the clinical aspects, laboratory findings, course and prognosis of acute infarction, but only a few papers have dealt with the mechanism of circulatory adjustment following the attack. Experimental studies by Orias<sup>1</sup> and by Gross, Mendlowitz and Schauer<sup>2</sup> have thrown some light on the subject. Orias concluded that the adaptability of the portion of the cardiac muscle not affected by the experimental infarction is the most important factor determining the outcome. Gross and his collaborators found a decreased cardiac output and increased circulation time indicating left ventricular failure. Fishberg, Hitzig and King<sup>3</sup> studied circulatory dynamics in human beings with acute myocardial infarction and found two distinct mechanisms influencing the course of the disease: (a) shock and (b) heart failure. They felt that in some cases one mechanism predominates and in others the other one. A more recent study

by Stead and Ebert<sup>4</sup> dealt with the same subject, and in it the authors emphasized the co-existence of both these factors in some of their cases. They expressed the opinion that both are manifestations of the same causative agent, which is diminished cardiac output following infarction. This cardiac, or "cardiogenic," mechanism of shock was discussed at length by Boyer<sup>5</sup> in a recent review. Grishman and Master<sup>6</sup> studied cardiac output by a physical formula and found it decreased after myocardial infarcts in 4 of their 5 cases. This was confirmed by Starr and Wood<sup>7</sup> who used the ballistocardiograph. Massie and Miller<sup>8</sup> found no changes in cardiac size by roentgenologic examination but noted signs of pulmonary congestion in most cases.

It is evident to all students of the subject that there are three distinct types of the disease, at least in the early stage following the acute attack: that of patients with predominant signs of severe shock, that of patients with dyspnea and pulmonary edema, often progressing into congestive failure, and that of patients without any symptoms and signs other than the initial attack of pain. While the first two types, being more dramatic, attract more attention in research, the third one is equally important from the practical viewpoint. Patients with severe shock or with cardiac failure show the highest mortality, and most of those who survive become cardiac invalids from chronic insufficiency. The milder, asymptomatic form of the disease is the one in which a high percentage of the patients recover. For these patients the attending physician faces a considerable responsibility, having to decide the length of rest in bed, the duration of con-

4 Stead, E. A., Jr., and Ebert, R. W. Shock Syndrome Produced by Failure of the Heart, *Arch Int Med* **69** 369-383 (March) 1942.

5 Boyer, N. H. Cardiogenic Shock, *New England J Med* **230** 226, 1944.

6 Grishman, A., and Master, A. M. Cardiac Output in Coronary Occlusion Studied by Wezler-Boger Physical Method, *Proc Soc Exper Biol & Med* **48** 207, 1941.

7 Starr, I., and Wood, F. C. Studies with Ballistocardiograph in Acute Cardiac Infarction and Chronic Angina Pectoris, *Am Heart J* **25** 81, 1943.

8 Massie, E., and Miller, W. C. Heart Size and Pulmonary Findings in Acute Coronary Thrombosis, *Am J M Sc* **206** 353, 1943.

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1 Orias, O. The Dynamic Changes in the Ventricles Following Ligation of the Ramus Descendens Anterior, *Am J Physiol* **100** 629, 1932.

2 Gross, L., Mendlowitz, M., and Schauer, G. Hemodynamic Studies in Experimental Coronary Occlusion, *Am Heart J* **13** 647 and 664, 1937, **14** 21 and 669, 1937, **16** 278, 1938.

3 Fishberg, A. M., Hitzig, W. M., and King, F. H. Circulatory Dynamics in Myocardial Infarction, *Arch Int Med* **54** 997 (Dec) 1934.

valescence and the completeness of occupational rehabilitation

This study deals largely with the milder form of the disease in an attempt to observe the derangement of the circulatory dynamics in patients so affected. Of the two major phenomena of myocardial infarction, shock and cardiac insufficiency, the latter is more important from the long range point of view. Shock is an acute incident responsible for many early deaths, but it disappears completely if the patient is to survive. On the other hand, signs of cardiac insufficiency in the ordinary sense may persist and progress into a chronic stage, and their presence or absence will determine the degree of the patient's recovery. Thus, even if those who believe in the common origin and identical mechanism of shock and congestive failure are correct, it is obvious that shock ceases to play a part in the course of myocardial infarction after the first few days. The fact that myocardial infarction affects almost exclusively the left ventricle is well known, and it is not surprising, therefore, that signs of left ventricular insufficiency are the predominant clinical features in this disease. The most sensitive method of detecting early left ventricular failure is determination of the velocity of blood flow through the pulmonary circulation.

#### METHODS AND RESULTS

The subjects studied were 45 unselected patients with acute myocardial infarction. Patients were observed personally and were included only if the diagnosis was reasonably certain, if the infarction was thought to be very recent and if they survived for more than a week after admission to the hospital. Particular attention was given to clinical signs and symptoms of left ventricular insufficiency, namely, paroxysmal dyspnea, orthopnea, gallop rhythm, pulsus alternans, basal pulmonary rales, hydrothorax and accentuation of the second pulmonic sound. The arm to tongue circulation time was measured by the bile salts method. 5 cc (or 3 cc for women) of a 20 per cent solution of sodium dehydrocholate (Procholon)<sup>9</sup> was rapidly injected into the cubital vein, and the time from the beginning of the injection to the signal given by the subject on perception of bitter taste was recorded. Only determinations with a sharp and distinct endpoint were considered. Determinations of circulation time were repeated at frequent intervals during the patients' stay in the hospital, and they varied from two to eight recordings. In half the patients, serial recordings of vital capacity were also made.

Of the 45 patients in this series, 32 recovered clinically and left the hospital asymptomatic, 5 remained in congestive failure varying in degree, and 8 died. Only 2 patients showed definite signs of shock.

Table 1 summarizes the results. They are based on two sets of figures: the shortest circulation time recorded during the first week after

the attack and the last recording made before the patient left the hospital. Values for circulation time were classified arbitrarily as normal (10 to 16 seconds), borderline (17 to 20 seconds), slightly prolonged (21 to 25 seconds), moderately prolonged (26 to 35 seconds) and definitely prolonged (over 35 seconds). Change in the circulation time was considered significant when it was 3 seconds or more in the first two classes and 5 or more in others. The table indicates that the initial reading was within normal limits in only 3 cases, with borderline values in 14, and was prolonged in 28. All patients who did not recover clinically showed prolonged circulation times at the time of their admission. Twenty-nine patients, including 24 out of the 32 with clinical recovery, showed shortening of the circulation time on subsequent determinations. Of the 13 remaining, 5 showed shortening of the

TABLE 1—*Circulation Time in Relation to Clinical Result\**

Circulation Time	Unim		Died	Total
	Recovered	proved		
Normal (10 to 16 seconds)	3 (1)	0	0	3 (1)
Borderline (17 to 20 seconds)	14 (10)	0	0	14 (10)
Slightly prolonged (21 to 25 seconds)	11 (9)	2 (1)	3 (0)	16 (10)
Moderately prolonged (26 to 35 seconds)	4 (4)	1 (0)	4 (1)	9 (5)
Definitely prolonged (Over 35 seconds)	0	2 (2)	1 (1)	3 (3)
Total	32 (24)	5 (3)	8 (2)	45 (29)

\* The figure on the left is based on the shortest circulation time recorded during the first week after the attack, the figure in parentheses indicates shortening of the circulation time on subsequent determinations.

circulation time coinciding with the initial improvement, but they died or had relapses later on. An additional analysis of the group of patients who recovered clinically showed that out of the 24 in which the circulation time became shorter with recovery, in 15 its final values were within normal limits, in 8 there were borderline readings and in 1 only did the circulation time remain above 20 seconds in spite of clinical recovery.

For 15 patients recordings of circulation time were made frequently enough to allow discovery of the approximate time after the attack when the final (or shortest) values were reached. These occurred at the end of the first week in 2 patients, during the second week in 4 patients, during the third week in 4 patients and during the fourth week in 5 patients.

For 22 patients serial determinations of vital capacity were made. Because of the influence of many noncardiac factors on the vital capacity,

<sup>9</sup> The E. R. Squibb Co. furnished a generous supply of Procholon for this study.

10 normal values were set, and the method was used only to observe changes in the same person after a myocardial infarction. These changes were found to be related to changes in circulation time. Table 2 presents the initial and the final readings of vital capacity and of circulation time in the 15 patients out of the 22 who recovered. It shows that in 9 of them there was parallel improvement evidenced by both methods, the increase in vital capacity corresponding to shortening of circulation time, in 4 circulation time but not vital capacity improved, and in 2 some improvement of the vital capacity occurred, while the circulation time was unchanged.

The longest circulation time after a myocardial infarction was for some patients registered within twenty-four hours after the attack, while in others

TABLE 2—Comparative Changes in the Circulation Time and Vital Capacity at the Onset and at the End of the Period of Observation

Patient	Initial Reading		Final Reading	
	Vital Capacity, Cc	Circulation Time, Seconds	Vital Capacity, Cc	Circulation Time, Seconds
J N	3,000	24	3,700	16
M C	2,000	26	2,200	15
R B	1,600	19	2,600	14
J A	3,200	25	3,200	16
J C	1,100	34	2,600	18
V S	3,500	20	3,500	17
R T	3,000	20	3,000	15
F W	1,700	15	2,000	14
J O	2,500	22	3,100	16
H O	3,400	19	3,400	14
T H	2,200	18	2,600	14
J G	1,100	16	1,100	16
F H	2,000	33	2,600	23
E S	2,700	18	3,100	17
C C	2,300	25	2,600	17
Average	2,350	22.3	2,700	16.1

it occurred some days afterward. In 10 patients the determinations were spaced very closely in the first week of the disease, and it was found that in 6 the peak was reached in twenty-four hours, in 1 after forty-eight hours and in 3 three days after the attack.

All the patients were divided according to the presence or absence of clinical signs and symptoms of cardiac insufficiency. In the group in which these features were evident, the initial circulation times in seconds were as follows: 16, 20, 20, 21, 21, 22, 22, 25, 25, 25, 28, 31, 31, 33, 34, 35, 35, 42 and 50, being 19 cases in all, with an average circulation time of 28 seconds. In the remaining 26 cases, without any circulatory insufficiency, the results in seconds were 15, 16, 17, 17, 17, 18, 19, 19, 20, 20, 20, 20, 21, 21, 22, 22, 22, 24, 24, 25, 25, 26, 26 and 36, with an average of

21.4 seconds. Even though this figure is significantly smaller than the one in the first group, as it was expected, it is still more than 50 per cent higher than the normal average of 13 seconds.

#### COMMENT

It is generally accepted that measurement of the arm to tongue circulation time is a valuable method of estimating the velocity of blood flow through the pulmonary circulation. This is based on the knowledge that the time from the injection of the substance into the vein to its entrance to the right side of the heart and the time of its flow from the left side of the heart to the receptor organ are both very short, so that most of the "circulation time" in the usual sense is spent on the flow through the lesser circulation, particularly through the pulmonary capillaries. The circulation time consists of four segments: the three just named and the reaction time, which is the time from the moment the fastest flowing particles of the substance arrive in the receptor organ until a sufficient concentration of them accumulates to stimulate the organ. The reaction time is negligible in normal subjects with the use of the proper technic, namely, the fastest possible injection of the substance into the vein. The slower the velocity of the blood flow, the more diluted is the substance, requiring longer time to stimulate the end organ and thus causing an additional delay in the circulation time in pathologic cases.

Numerous methods of measuring the circulation time are being used. In all of them an indifferent foreign substance is injected into the vein. The arrival of the substance in the receptor organ is recognized (a) by the patient's subjectively perceiving an abnormal sensation (bitter or sweet taste or heat sensation), (b) by objective signs such as cough or sighing respiration and, finally, (c) by means of specially devised detectors, as for example, for radioactive substances or for fluorescein. Most of the methods used are fairly reliable, although errors occur occasionally, mostly due to an exaggeration of already definitely prolonged circulation times by dilution of the substance. The recent reports by Lilienfeld and Berliner and Esser and Berliner<sup>10</sup> demonstrating discrepancies of duplicate readings of circulation time are not confirmed, particularly for normal or for slightly prolonged readings.

10 Lilienfeld, A., and Berliner, K. Duplicate Measurements of Circulation Time Made with Alpha Lobeline Method, *Arch Int Med* 69:739 (May) 1942. Esser, K. H., and Berliner, K. Duplicate Measurements of Circulation Time with the Saccharine Method, *Ann Int Med* 19:64, 1943.

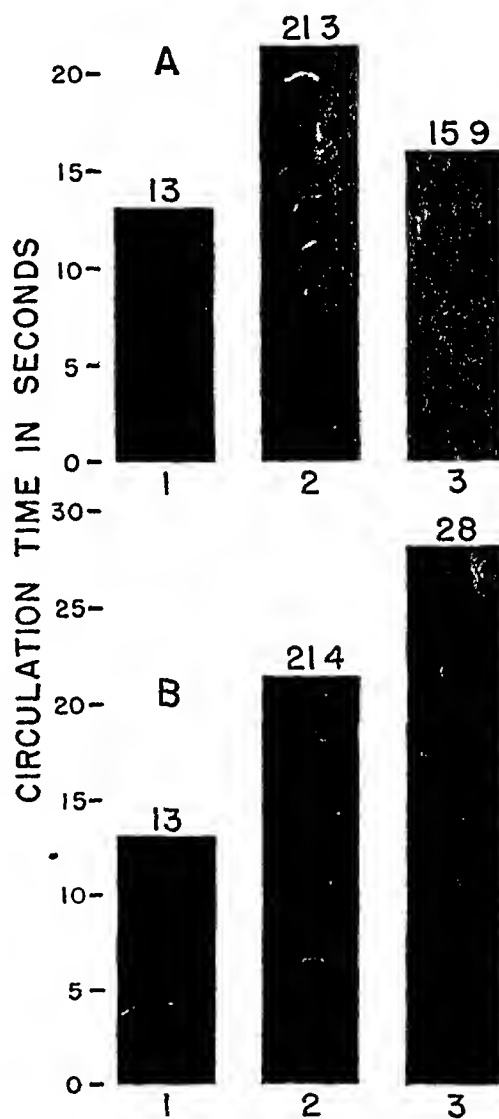
One of the methods they used is shown to be unreliable (alpha lobeline hydrochloride)<sup>11</sup>

Determination of circulation time is thus a generally accepted clinical method of measuring the velocity of the blood flow through the pulmonary circulation and may be considered accurate and reliable when used judiciously. It appears, however, that its accuracy decreases with the lengthening of the circulation time when to the low velocity of blood flow due to cardiac insufficiency other factors are added. These factors not only lengthen unduly the time but also introduce a variable element obscuring the relation of circulation time to cardiac function and to the clinical course. For instance, when 2 patients with cardiac insufficiency show circulation times of 30 and 60 seconds, it is doubted whether in the second patient the velocity of the blood flow is actually slowed twice as much as in the first.

In this study most of the patients had only slightly or moderately prolonged circulation times, which are in the range of the sensitivity and reliability of the method. Therefore the statistical significance and accuracy of the data appear unquestionable.

It appears from the results presented that in early stages of acute myocardial infarction there is a definite increase in circulation time, which means slowing of the pulmonary circulation. This fact indicates that left ventricular insufficiency is the rule in almost all cases, even though it is clinically apparent in only a few. As healing of the infarct takes place, the cardiac function improves, and the circulation time usually returns to normal or to borderline values. This is presented graphically in the chart (A). The chart (B) also presents the values for circulation time of patients with clinically evident left ventricular failure contrasted with those of patients without symptoms of cardiac insufficiency. The fact that in asymptomatic patients the value is decidedly increased, though shorter than in the first group, is the most important finding of this study. It fits in with the result of roentgenographic demonstration of latent left ventricular failure in cardiac infarction by Massie and Miller.<sup>8</sup> Roentgenologic demonstration of left ventricular insufficiency by presence of pulmonary congestion, though helpful, is a less constant and less sensitive measure than the circulation time.

The absolute values of individual results are somewhat diminished by the presence of apparently insignificant delays in the circulation in some cases, even though the statistical value of the group as a whole is obvious. The presence of so many borderline readings can be explained first of all by the overlapping of normal and pathologic results in individual cases. For example, if a patient with a normally high velocity blood flow (around 10 seconds) develops a myocardial infarction, his circulation may slow by 60 per cent without bringing the reading outside



A Average circulation time (1) normal value, (2) initial value in patients who recovered from myocardial infarction and (3) final value in the same group of patients

B Average circulation time (1) in normal persons, (2) in patients without clinical signs and symptoms of left ventricular failure after myocardial infarction and (3) in those with obvious left ventricular failure

the normal limits of 16 seconds. Difficulty in evaluating normal results because of wide individual variations occurs in many other clinical methods. This is exemplified in the data on vital capacity, for which no normal standards were set at all. This method could be used only

11 Hussey, H. H., Cyr, D. P., and Katz, S. The Comparative Value of Calcium Gluconate, Magnesium Sulfate and Alpha-Lobeline Hydrochloride as Agent for Measurements of Arm-to-Tongue Circulation Time in Fifty Patients With and Fifty Patients Without Heart Failure, *Ann Int Med* 17:849, 1942.

for studying the same person, and comparison of the readings in different persons is of no value at all

To this factor of overlapping of normal and abnormal values another one may be added which also tends to divert the average circulation time toward normal, and that is the possible effect of noncardiac factors on the velocity of the blood. It is well known that in hypothyroidism and polycythemia the circulation is slowed, while in anemia and hyperthyroidism velocity is increased. Other causes of shortened circulation time are fever, exercise and excitement with tachycardia. The effect of fever or of excitement due to pain may play a considerable part in counteracting the slowed circulation from cardiac insufficiency. This series of patients is too small to demonstrate conclusively this relation, but one can speculate about the possibility that these factors could account for the failure to demonstrate significant delays in circulation in all 45 of them.

The use of data on vital capacity proved of considerable value in corroborating changes in the circulation connected with healing of the infarct by another independent method, but determination of circulation time appears to be more reliable and simpler for routine use.

Thus it is demonstrated that after an infarction of the heart a strain develops on the remaining healthy muscle of the left ventricle, which is the part of the heart almost exclusively affected by infarction. The result is left ventricular insufficiency, which in milder forms may be slight and latent and in severe ones obvious and even irreversible. As healing progresses, an adjustment and adaptation of the function of the left ventricle results, in most cases, in a return of the circulation time to normal or to borderline values. The initial derangement of the circulation after the insult may appear immediately or after a period of hours or days. This variable interval, incidentally, also occurs in some other phenomena of infarction, such as drop in blood pressure.

It is felt that the result of this study is of more than academic interest. It may be applied in selected cases as an aid in diagnosis and prognosis of myocardial infarction. The observation that the circulation time is prolonged in myocardial infarction may help to differentiate this from other conditions associated with similar attacks of pain in the chest. This differential diagnosis is often difficult, especially when the electrocardiogram is equivocal, as in atypical infarcts or in those associated with bundle branch block. In some such cases it may be difficult to decide whether the pain originates in the heart

or in other organs and, if in the heart, whether it is due to an infarction of the myocardium, to transient coronary insufficiency or to pericarditis. In many patients a determination of the circulation time may offer an important clue, particularly when the reading is either definitely prolonged or very short. For instance, if the diagnosis is in doubt, a circulation time of 24 seconds would make the diagnosis of infarction very likely, as in no other condition associated with pain in the chest is there a cause for slowing of the pulmonary circulation in the absence of obvious heart failure. On the other hand, in a similar case with a circulation time of 11 seconds other diagnoses than cardiac infarction should be considered, especially when fever and tachycardia are absent.

Recent studies by Barnes and Burchell<sup>12</sup> and by Wolff<sup>13</sup> dealing with acute pericarditis have shown the difficulty of distinguishing this condition from myocardial infarction. Here the value of the determination of circulation time in the differential diagnosis may be of particular interest.

While a single determination of the circulation time is useful in the differential diagnosis of myocardial infarction, serial readings may help determine the progress of the patient recovering from it. In patients who after the initial attack of pain present no signs and symptoms there is no clinical indication as to the satisfactory healing of the lesion. Laboratory procedures are often not helpful and may even be misleading. For instance, electrocardiographic evidence of changes may persist for months or even become permanent, regardless of the clinical condition of the patient. Fever and leukocytosis last only a short time. The sedimentation rate may be increased for many weeks after the patient is apparently well, but this persistence does not necessarily indicate deficient healing. Therefore, study of the circulatory readjustment after a myocardial infarction offers a method of observation of the convalescing patient by estimation of the most important single factor in recovery—the function of the left ventricle. The method has the great advantage of being simple, safe and inexpensive and does not require any special equipment. It is logical to assume that a patient with a more noticeable initial slowing of the circulation time and a slower rate of accelera-

12 Barnes, A. R., and Burchell, H. B. Acute Pericarditis Simulating Acute Coronary Occlusion. Report of Fourteen Cases, *Am Heart J* **23** 247, 1942.

13 Wolff, L. Acute Pericarditis Simulating Myocardial Infarction, *New England J Med* **230** 422, 1944.

tion ought to be hospitalized longer than the one who shows a mildly prolonged circulation time which returns to normal in a few days

#### SUMMARY

Forty-five unselected patients with acute myocardial infarction were studied by serial determination of the arm to tongue circulation time and 22 of them also by serial determinations of vital capacity. The results were correlated with the clinical observations and with the course of the disease.

In all but 3 patients the initial readings of the circulation time were above normal, the average value for the series being 24.3 seconds (normal 13 seconds). In 24 of the 32 patients who recovered clinically there was a significant decrease in the circulation time on subsequent readings.

Prolonged circulation time indicating left ventricular failure was found most definitely in patients with clinical evidence of cardiac insufficiency (19 patients with an average value of 28 seconds), however, in patients who were entirely asymptomatic except for pain there was still a definite delay, indicating latent left ventricular failure (26 patients with an average of 21.4 seconds).

Determinations of circulation time are of practical value and are thought to be worth while as a routine procedure in myocardial infarction (*a*) as an aid in diagnosis by helping to differentiate it from other conditions associated with pain in the chest and (*b*) in evaluating the progress of circulatory readjustment after an infarction by means of repeated determinations of circulation time.

## Correspondence

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### PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

*To the Editor* —I should like to present the following concept of pernicious anemia and related macrocytic anemias for the consideration of your readers

Just as pellagra is no longer considered a "disease" of the skin, gastrointestinal tract or nervous system but is classified rather as a vitamin deficiency disorder, manifested by a disturbance in the metabolism of probably every tissue cell, so, too, the known facts relating to pernicious anemia may be construed to define not a "blood disorder" but one which affects the metabolism of diverse systems of the organism

Thus, the "intrinsic factor," possibly an enzyme secreted into the stomach (Lasch [1937], Taylor [1938], Gessler [1940]), acts on the "extrinsic factor," possibly some portion of the vitamin B complex (Goodall [1932], Ungley [1933 and 1934], Strauss [1932], Wintrobe [1939]), with the resultant formation of a thermolabile substance which is conveyed to the liver by way of the blood stream. The liver then transforms this thermolabile substance into a thermostable compound, namely, "liver extract principle." Thus the liver functions not merely as a storage organ but as an active participant in the elaboration of liver extract principle

I am also suggesting that "liver extract principle" is in reality a vitamin, which is possibly concerned with the proper functioning of some enzyme system, in a manner similar, perhaps, to that of nicotinamide, which is involved in enzyme reactions by way of coenzymes I and II (diphosphopyridine and triphosphopyridine nucleotides)

If such a function is conceded for "liver extract principle," the widespread disturbances of pernicious anemia—the gastrointestinal, the nervous, even the blood picture itself—then become readily explainable

on the basis of a disordered metabolism involving one or more particular enzyme systems with which "liver extract principle" is intimately concerned

If the "intrinsic factor" is absent or deficient, as occurs in so-called true Addisonian pernicious anemia and in high gastric resection (Bence [1934], Goodman [1935]), no thermolabile factor can be formed and deficiency of "liver extract principle" results

If the "extrinsic factor" is lacking, as may occur in certain instances of macrocytic anemia, again no thermolabile factor is produced and deficiency of "liver extract principle" results

If the thermolabile factor is formed, by interaction of "intrinsic" and "extrinsic" factors, but is not absorbed, owing to increased intestinal impermeability, as may occur in sprue, or owing to gastrointestinal short circuits, the thermostable factor cannot be formed and again a deficiency of "liver extract principle" results

If the thermolabile factor is absorbed and conveyed by the blood stream to the liver, thermostable "liver extract principle" can result only in the presence of a liver which is functionally adequate to elaborate "liver extract principle." It is possible that in those instances in which macrocytic anemia, associated with other bodily disorders, occurs in the presence of hepatic damage, as in certain cases of hepatic cirrhosis, this function of the liver is disturbed and deficiency of the thermostable principle results

Recent work indicates that the active principle of liver will soon be isolated and its structure determined. And with this the syndrome of macrocytic anemia will be removed from the category of "blood diseases" and added to the list of vitamin deficiency disorders

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## Book Reviews

**Hypertension and Hypertensive Disease** By William Goldring, M D, and Herbert Chasis, M D Price, \$3.50 Pp 253 New York Commonwealth Fund, 1944

The authors are well qualified to write a book on hypertension and hypertensive disease. They possess abundant clinical experience and are thoroughly familiar with the fundamental research work which has contributed so greatly to the recent advances in the study of hypertension.

During the past ten years, the progress made in the knowledge of hypertension and especially of hypertensive disease has resulted from a combined study of clinical work and laboratory research. The newer methods employed to investigate the changes both in renal function and in renal hemodynamics are intricate and may be confusing to any one unacquainted with them. However, the authors have explained these newer procedures in an adequate and simple manner.

The main part of the book deals with the evolution of the functional changes in the course of hypertension and hypertensive disease. The authors' concept of the genesis of hypertension, with special reference to the role of the kidneys, is given. From their investigations, they point out that the relationship between ischemia of the kidneys and hypertension is not the simple and direct cause and effect relationship that one would believe from experimentation with animals. Their conclusions are based not on research on animals but on a study of hypertensive persons. They believe that renal ischemia is one of the sequelae of hypertension and not a cause.

The renal genesis of hypertension in man can be accepted only in cases in which a pathologic process, such as diffuse glomerulonephritis, polycystic renal disease or atrophic pyelonephritis, involves both kidneys.

In their study of hypertensive patients, they used quantitative measurements of effective renal blood flow, filtration rate and maximal tubular excretory capacity. The earliest changes that occur in renal function and in renal hemodynamics are reduction in the maximal tubular excretory capacity, an associated reduction in renal blood flow and an increase in the filtration fraction. Such functional tests as those of urea clearance and of excretion of phenolsulfonphthalein are not altered in this early phase.

Changes that occur in the heart, the brain, the eye-grounds and the kidney are taken up and evaluated from the clinical standpoint.

A satisfactory amount of space is devoted to treatment. For any one looking for the authors' favorite prescription or method of treatment, there will be disappointment. Treatment is divided into medical, surgical and special measures. The authors' attitude from the therapeutic standpoint is rather nihilistic but probably deservedly so. They have no confidence in potassium thiocyanate as a therapeutic drug, opposing it chiefly on the grounds of the serious toxic complications which may develop. They believe that surgical operations, such as sympathectomy and similar procedures, have little or nothing to offer. They do, however, emphasize the importance of and the good results obtained from use of psychotherapeutic measures. The value of renal extract is believed to be uncertain.

This book is well written and easy to read. An intern, surgeon, urologist or any other person interested in hypertension will find an excellent discussion of the subject in this book. In the reviewer's opinion, the lessons contained in the book confirm the idea that the clinical study of hypertension cannot be separated from the more elaborate investigations carried out in the laboratory. Both must be integrated for a complete study of the disorder.

This is the first book of its kind which integrates the clinical and investigative phases of hypertension, and it is an important and excellent contribution to the subject.

**Trichinosis** By Sylvester E. Gould, M D Price, \$5 Pp 322, with 128 illustrations Springfield, Ill Charles C Thomas, Publisher, 1945

The relative frequency of infestation of the adult population with *Trichinella spiralis* has been readily demonstrated by postmortem surveys. The relatively infrequent incidence of clinical trichinosis must result, therefore, from our failure to recognize sporadic cases, as it can manifest itself frequently with unusual symptomatology.

A complete treatise on this disease is a valuable contribution to current medical literature. This is a well written work embodying several interesting features, including historical aspects, parasitology, pathology, epidemiology, clinical aspects, treatment and control measures. One must call special attention to the section on the morphology of *Trichinella spiralis*, which includes several excellent illustrations and magnifications of microscopic studies.

In the section on epidemiology stress is placed on the pernicious practice of feeding pigs uncooked garbage containing scraps of raw trichinous pork, thus maintaining the pig as a reservoir for further human infection. The cycle then continues when uncooked or undercooked trichinous pork or pork products are eaten.

In his chapter on control measures, the author outlines how this cycle of transmission of infection might be attacked at several vulnerable points: first, by not permitting the feeding of swine with uncooked garbage, then, by encouraging proper inspection of pork and pork products, and, finally, by educating people to the fact that pork which is pink has not been sufficiently cooked and that pork which is not thoroughly cooked should not be eaten.

In the section on symptomatology it is pointed out that the varied clinical picture of trichinosis is only a reflection of the widespread distribution of parasites in the body, although generally the phases of the disease may be classified as the intestinal stage, the stage of muscular invasion and the stage of convalescence. Not infrequently the onset may be respiratory in nature, with coryza, cough and dyspnea. Neurologic symptoms which are common are supraorbital headache, vertigo, tinnitus and insomnia. Related to the involvement of the cardiovascular system is generally myocarditis, which may appear as early as the second week. This is probably on a toxic basis, since the larvae of *Trichinella spiralis* have never been found to be encysted within the heart muscle. The symptoms are substernal or precordial pain, tightness in the chest, shortness of

breath and palpitation. An important differentiation must be made between the edema of myocardial failure, which appears between the fourth and the eighth week, and the edema of the muscles of inflammatory origin, which will have begun to subside or will have disappeared by that time.

This book, complete in every detail, remains readable throughout. It includes a comprehensive bibliography, which enhances its value as a reference work.

**Hipertensión arterial nefr6gena** By Eduardo Braun-Menendez and associates. Price, not given. Pp 475, with 93 illustrations. Buenos Aires, Argentina. Libreria y Editorial "El Ateneo," 1943.

In this book the authors give a review of their own experimental investigation and clinical experience, a digest of most of the modern works of other investigators and a comprehensive picture of the whole problem of arterial hypertension. Through their own experiences, they are well prepared to write a book such as this. The main part of the book deals with the genesis of renal arterial hypertension in man and in animals. The writers conclude that hypertension in man is not identical with the hypertension found in the experimental animal, and they emphasize the anatomical differences between the two forms.

Considerable space is devoted to the results of their pioneer investigations on renin, hypertensinogen and hypertensin. In brief, they hold to the theory that renin plus hypertensinogen produces hypertensin (angiotonin), which is responsible for the arteriolar constricting that produces hypertension. They discuss the enzyme hypertensinase, a substance from the kidney, which destroys hypertensin and allays arteriolar constriction. A careful account is given of the therapeutic possibilities of their own renal extract containing hypertensinase, and of the extracts of others, such as that of Page.

A special section of the book is given over to the etiology, clinical features and treatment of renal arterial hypertension in man. The action of various drugs, extracts and other agents used to reduce blood pressure is carefully and satisfactorily discussed.

Surgical procedures, such as removal of tumors of the kidney and correction of other conditions of the kidney, as well as operations on the adrenal gland and on the sympathetic nervous system, are taken up. Like most other authors, they believe that operations on the sympathetic nervous system for the control of hypertension have limited possibilities.

In this book there is a wealth of information on various problems of hypertension as well as a rich bibliography. It is well written, and there are many valuable illustrations and charts and an excellent page of colored photomicrographs. This is an excellent book, but it should be of more value to the investigator of the problem of hypertension than to the general practitioner.

**Familial Susceptibility to Tuberculosis. Its Importance as a Public Health Problem.** By Dr Ruth Rice Puffer. Price, \$2. Pp 106, with 9 figures and 24 tables. Cambridge, Mass. Harvard University Press, 1944.

This monograph stresses the importance of familial susceptibility in the development of active tuberculosis. The conclusions are reached by statistical analysis, and much of the material dealt with has been accumulated through the Williamson County Tuberculosis Study.

This project was undertaken in Williamson County, Tenn., in 1931, with the assistance of the International Health Division of Rockefeller Foundation.

It is stated that more persons from families susceptible to tuberculosis appear to contract the disease than do persons from resistant families and that they have a more severe form. The suggestion is made that familial aggregation of tuberculosis has remained relatively stationary and that the decline in the tuberculosis death rate is due to a reduction in the proportion of tuberculous families in the population. There are interesting observations on the tuberculosis attack rate in children of tuberculous parents. This rate was high up to age 30 when the parent was known to have organisms in the sputum. In the children of tuberculous parents not known to have organisms in the sputum, active disease developed later, and by the age of 50 total attack rate in the two groups was equal. This would imply that with less exposure to tubercle bacilli the susceptible person contracts the disease later in life. The continued decrease in the incidence of tuberculosis might account for the relatively greater mortality rate of this disease in older age groups which has been observed in recent years.

In the chapter on the control of tuberculosis it is recommended that, in addition to the examination of the household contacts of persons with tuberculosis, the parents, siblings and children not in the household be followed and examined periodically. There is some question as to how feasible this would be with members of families widely scattered. An explanation of the statistical methods used is included in appendix B. The book can be read with profit by any physician interested in the problems of control of tuberculosis.

**The Doctor's Job** By Carl Binger, M.D. Price, \$3. Pp 243. New York. W. W. Norton & Company, Inc., 1945.

Perhaps the keynote of Dr Binger's book is to be found in the introduction when he says, "I am setting down these thoughts now because I feel the need of doing so." In other words, this is a simple, straightforward interpretation of medicine and its problems as one man sees them. Dr Binger writes "on his own." He represents no foundation, forum, group or panel. He speaks for no organized interests of any sort. There are no political angles to his book. None the less, all the problems of medicine, so much under debate at the present time, are discussed in a sympathetic, well reasoned manner. Dr Binger talks about general practice and specialization and conceives that some one must again take up the burden once borne by the family doctor. This man will not do everything himself but will "route" the patient to the proper specialists and finally will synthesize and interpret the whole situation. There are chapters on various disorders, usually with some emphasis on the psychosomatic aspects, and one finds discussions on forms of practice, socialized medicine and so forth.

In these days when the language is likely to be pretty badly abused in medical writing, Dr Binger's style is a delight. Clearness, force and precision—the three graces of rhetoric—are set off by those decorations of language which, if properly used, add so much to the reader's pleasure—the apt quotation, the crisp aphorism, the *mot juste*. From the literary standpoint alone this book can be enjoyed equally by physician and layman.

## POWDERED STOMACH IN TREATMENT OF FATTY LIVER AND OTHER MANIFESTATIONS OF INFANTILE PELLAGRA

ITS SIGNIFICANCE WITH REFERENCE TO THE PROBLEMS OF EDEMA AND STEATORRHEA IN INFANTS AND IN ADULTS

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The syndrome which we accept provisionally as pellagra in infants is prevalent among the non-European children in Johannesburg. An analysis of the hospital records during the last four years has revealed that the death rate among children suffering from this disease fluctuates between 40 and 60 per cent irrespective of the nature of the treatment administered. Even vitamin concentrates given parenterally did not in any way diminish this high mortality rate.

The views generally held concerning the causes of pellagra<sup>1</sup> seem to suggest that this disease is in some way caused by a lack of vitamin B complex, especially of nicotinic acid. However, the failure of vitamins in approximately 50 per cent of cases added support to our hypothesis that after a variable latent period a disease initiated by a dietary deficiency fails to respond when the factor whose deficiency is suspected to cause the disease is supplied liberally.

The rather complicated clinical picture presented by these children obliged us to search for that mechanism the disturbance of which could account for the edema, steatorrhea and other reactions frequently present in this disease. In a previous study<sup>2</sup> we indicated that the liver was invariably damaged to a greater or lesser extent, as shown by the accumulation of abnormal quantities of fat. Irrespective of the clinical

state of the patients or the biochemical findings, the prognosis was largely determined by the severity of the hepatic injury, assessed by histologic examination of fragments of liver obtained by the aspiration biopsy technic<sup>3</sup>.

It soon became clear that the disturbances in the functions of the liver perhaps contributed in no small measure toward the production of many of the manifestations of infantile pellagra. By means of the aspiration biopsy technic we established beyond reasonable doubt that the fatty liver in pellagrins does not result from intercurrent infections but is one of the manifestations of dietary imbalance.

Experiments on animals indicated that, while the lack of a specific vitamin from the diet caused a fatty liver, the addition of this vitamin frequently failed to alleviate this pathologic process and in fact, under certain circumstances, even intensified the lesion<sup>4</sup>. It was also demonstrated that the fatty liver produced in animals by the lack of a vitamin could be cured by the addition of some substance other than the vitamin, namely, methionine<sup>5</sup>.

These findings in animals received confirmation from our studies of the effects of vitamins on the fatty livers of human infants suffering from pellagra. We were able to show that in infantile pellagrins with intensely fatty livers, vitamin therapy could not reduce the death rate or heal the hepatic lesion. Even when hepatic damage was mild, although the clinical condition

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J Inglis, L Friedlander and E Hammar of the Johannesburg General Hospital gave assistance.

1 Stannus, H S. Pellagra and Pellagra-Like Conditions in Warm Climates, *Trop Dis Bull* 33 729 (Oct), 815 (Nov) 1936. Elvehjem, C A. Relation of Nicotinic Acid to Pellagra, *Physiol Rev* 20 249 (April) 1940.

2 Gillman, T, and Gillman, J. Hepatic Damage in Infantile Pellagra and Its Response to Vitamins, Liver and Ventriculin Therapy as Determined by Repeated Liver Biopsies, to be published.

3 Gillman, T, and Brydon, J G. To be published.

4 Handler, P, and Dann, W J. Inhibition of Rat Growth by Nicotinamide, *J Biol Chem* 146 357 (Dec) 1942.

5 Engel, R W. The Relation of B-Vitamins and Dietary Fat to the Lipotropic Action of Choline, *J Nutrition* 24 175 (Aug) 1942. McHenry, E W, and Patterson, J M. Lipotropic Factors, *Physiol Rev* 24 128 (Jan) 1944.

improved under therapy, the recovery of the liver was slow, and the patients left the hospital with residual damage to the liver. We discovered that powdered stomach led to a rapid improvement in the clinical condition and simultaneously depleted the fat from the liver.

The fact that powdered stomach, a substance not related to any of the known vitamins, was able to cure infantile pellagra afforded us an opportunity of examining the various mechanisms involved in the production of several of the clinical features of this disease in relation to the fatty liver.

The objects of this paper are, firstly, to record the clinical and biochemical findings in 23 cases of infantile pellagra before and after various forms of treatment, secondly, to assess the relation between the pathologic changes in the liver and the clinical picture, thirdly, to examine the factors responsible for the edema and steatorrhea prevalent in this disease, and, fourthly, to comment on the implications of the edema and steatorrhea in modifying the course of the disease. Finally, in view of the similarities between infantile pellagra and those other diseases of infants and adults characterized by steatorrhea, edema and anemia, we will attempt to show that all these diseases, though differently caused, probably follow the same course once the steatorrhea appears, owing to the disturbance of a similar physiologic mechanism.

#### MATERIAL

This report is based on the study of 23 infants and children suffering from pellagra who were admitted to the Johannesburg Non-European Hospital during the summer of 1943-1944 and the autumn of 1944.

Aspiration biopsies of the liver were performed on all these patients within a few hours of admission, and whenever possible blood was withdrawn for hematologic, biochemical and serologic examination. For 9 patients who passed bulky fatty stools estimations of the water and of the split and unsplit fat content were made. Examinations of urine were made in every instance to exclude severe renal damage.

Full clinical records of the history of the disease, diet and clinical signs were kept. The children were weighed on admission and daily thereafter during their stay in the hospital.

The first 7 patients were treated with vitamins orally and parenterally according to the details listed in the table. The next group of 7 were given injections of 5 cc of liver extract in the Cohn (anti-pernicious-anemia) frac-

tion<sup>6</sup> twice daily for ten days. The third group of 9 patients received 10 Gm of powdered stomach<sup>7</sup> orally, together with 5 cc of tenth-normal hydrochloric acid once daily. In view of the shortage of the drug, treatment with powdered stomach could be continued for only five days. All patients were fed a liberal diet.

Biopsy of the liver was performed on all the patients every seven to ten days after admission, and comparisons were made of the clinical progress and the changes in the histologic appearance of the liver.

#### CLINICAL FEATURES

The syndrome which was seen in the Johannesburg Non-European Hospital and which we regard as infantile pellagra is characterized by severe edema, typical cutaneous lesions, labial and angular stomatitis, glossitis, diarrhea or steatorrhea, peculiar depigmentation of the skin over the entire body and a graying of the hair of the scalp with varying degrees of alopecia.

A similar syndrome has been encountered in other parts of South Africa<sup>8</sup> but Trowell<sup>9a</sup> was the first to suggest that this syndrome called by different names was probably infantile pellagra.

Although Trowell<sup>9a</sup> and Kark<sup>8d</sup> have carefully recorded the majority of the features of this form of malnutrition in infants, there are several aspects of this disease which require further amplification, such as the seasonal incidence, the peculiar manifestations of some of the cutaneous lesions and, especially, the steatorrhea and the edema in relation to the hepatic damage, as revealed by the aspiration biopsy technique.

*Seasonal Incidence*—An analysis of over 400 cases of infantile pellagra in patients of the Johannesburg Non-European Hospital extending over a four year period reveals that, while the disease occurs throughout the year, the

6 The preparation used was an injectable liver extract (Abbott Laboratories) containing 10 U S P units per cubic centimeter.

7 The preparation given was ventriculin (Parke, Davis & Company).

8 (a) Williams, C. D. Nutritional Disease of Childhood Associated with Maize Diets, *Arch Dis Childhood* 8: 423 (Dec.) 1933. (b) Purcell, F. M. Diet and Ill-Health in the Forest Country of the Gold Coast, London, H. K. Lewis & Co., Ltd., 1939. (c) Macvicar, N. Pellagra in the Cis-Kei, South African M. J. 9: 892 (Dec. 25) 1935. (d) Kark, S. L. Adult and Infant Pellagra in South African Bantu. A Comparative Clinical Study, *South African J. M. Sc.* 8: 106 (July) 1943.

9 (a) Trowell, H. C. Infantile Pellagra, *Tr. Roy. Soc. Trop. Med. & Hyg.* 33: 389 (Jan.) 1940, (b) Pellagra in African Children, *Arch Dis Childhood* 12: 193 (Aug.) 1937.

greatest incidence is during midsummer and the lowest during midwinter. In this respect pellagra in infants resembles the disease in adults in Johannesburg.

*Dermatitis*—A description of the dermatologic reactions in infantile pellagra has been carefully recorded by Trowell and Kark.

In our selected series of 23 cases diffuse depigmentation associated with patchy pigmentation and scaling occurred in 10 patients, while in 4 there was ulceration of the buttocks, genitalia, legs, arms or trunk. An unusual and hitherto unrecorded lesion expressed itself as crops of dark brown raised spots on the upper and lower extremities, especially on the dorsal surfaces of the hands and feet. These spots closely resembled the purpuric eruption of onychia, a thrombopenic purpura frequently observed among the patients in this hospital.<sup>10</sup> However, the bleeding time was normal, and the subsequent extension of the lesions, followed later by cracking and desquamation of the skin in the affected areas, left little doubt that these spots were merely another manifestation of the pellagrous rash.

In severe infantile pellagra the exfoliation of the skin may be so extensive and so acute that large portions of the body are denuded. The exposed areas are raw, red and oozing and frequently become secondarily infected. These septic wounds are associated with such severe collapse that they have repeatedly been mistaken for severe burns or scalds.

*Tongue*—The raw, red beefy tongue of adult pellagrins is not seen in infants, instead the tongue is smooth and atrophic. A common phenomenon in adult pellagrins is an infiltration of the papillae on the tip, dorsum or sides of the tongue with black pigment. This has occasionally been recorded among colored races and has been regarded as a congenital abnormality or as a consequence of parasitic infections.<sup>11</sup> Kark regarded pigmentation of the tongue as a type of pellagrous glossitis. We have actually seen this pigment appearing during the healing of the raw, beefy tongue or of the magenta red tongue in avitaminosis. We are satisfied that this lesion is not a congenital abnormality, espe-

cially since we have never observed it in children under 10 years of age.

As we have already indicated, iron pigment first appears in considerable quantities in livers damaged by acute or long-standing chronic malnutrition in children over 9 years of age.<sup>12</sup> It is at this time, too, that the tongue also becomes pigmented. The metabolism of iron pigment undergoes a radical change at this age period (8 to 10 years), so that some forms of acute and chronic malnutrition may result in such a disturbance of intracellular metabolism in various organs and tissues in the body that iron-containing pigment is deposited in the hepatic cells and in the tunica propria of the tongue. We have already indicated that iron pigment deposited in the cells of the liver does not arise directly from destruction of blood but is formed in the cell itself.<sup>12</sup>

*Edema*—Edema of varying severity can be regarded as a constant finding in infantile pellagrins. It was present in 27 out of 29 patients described by Trowell,<sup>13</sup> and in 20 of 34 patients reported on by Kark the edema appeared in a severe form. In our series 21 patients manifested various degrees of edema. In nature and distribution this edema is similar to that described by Trowell, except that we never saw the edema abate before death and that in some boys the edema of the penis and prepuce was so severe that the generalized edema was attributed to renal failure resulting from a severe and prolonged paraphimosis. Before the disease was recognized in this hospital as infantile pellagra, circumcisions were frequently performed to relieve what was then regarded as a urethral obstruction. Many of these operations were attended by fatal results.

*Liver*—Although one of the most consistent conditions seen at autopsy in children dying from severe nutritional edema is an intensely fatty liver,<sup>14</sup> it is generally thought that this fatty change was a terminal event or the result of an intercurrent infection.

By means of the aspiration biopsy technique, we have established that a fatty liver is the most constant single pathologic reaction seen in infantile pellagra. It appears early in the disease and, as we shall indicate later, probably plays an important part in modifying the course of the disease. Even with the mildest symptoms we have never failed to find some degree of fatty change in the liver. Although the extent

10 Stein, H. B., and Miller, E. Acute Thrombocytopenic Purpura Associated with Hemorrhagic Bullae, with Special Reference to Onychia, South African J. M. Sc. 8:1 (Feb.) 1943.

11 McGregor, L. The Significance of the Butterfly Sign and of Tongue Pigmentation, Tr. Roy. Soc. Trop. Med. & Hyg. 30:482 (Jan.) 1937. Sundaram, S. K. The Butterfly Sign and Pigmentation of the Tongue, ibid. 30:482 (Jan.) 1937.

12 Gillman, T., and Gillman, J. The Mitochondrial Origin of Cystosiderin (Iron Pigment) in the Liver Cells of Pellagrins, Nature, London 154:148 (July 29) 1944.

of the fatty change in the liver varied from case to case, we have found that the degree of accumulation of fat is a more reliable indicator of the severity of the disease and of the prognosis than any of the clinical or biochemical findings. Thus, for example, in case 1 (described in the table) the clinical picture suggested a mild deficiency disease, whereas the biopsy revealed a severe lesion. This case terminated fatally.

In a previous communication we grouped the different degrees of hepatic damage into three categories.<sup>2</sup> In the first we included those livers in which almost all the cells contained single, large fat globules, in the second, the livers were less severely damaged and the fat occurred either as smaller globules staining more intensely with sudan IV (scarlet red) than in the first category or as diffusely distributed, multiple fine droplets. Many cells did not contain any fat. In the last category the fat was present in the form of fine, scattered droplets and then in only a few cells.

Our previous studies demonstrate that children with livers of the third category usually recovered after any form of rational therapy irrespective of the severity of the clinical picture, whereas the patients with livers of the first and second category frequently died unless treated with liver extract or, better still, with powdered stomach. Recovery was always accompanied by a diminution in the fat content of the liver.

The accumulation of fat causes an enormous enlargement of the individual hepatic cells. It was to be expected therefore that in our patients the livers would be enlarged. In 18 of 23 cases the liver was distinctly palpable (as shown in the table), and in 15 it extended almost to the umbilicus. In 1 instance, however, histologically the liver was included in the first category but clinically this organ was not palpable.

It must be remembered that in some of these malnourished children the abdomen is so distended that it is impossible to palpate even a grossly enlarged liver. When the liver is palpable, its size can be regarded as an extremely valuable evidence in assessing the severity of the disease and in arriving at an accurate prognosis.

The main clinical features of 23 cases of infantile pellagra are summarized in the table. It is apparent from this table that the clinical features and the severity of the lesions may vary from case to case. Whereas severe and extensive edema are frequently associated with severe cutaneous lesions (cases 2, 7, 10, 11, 13, 15, 19), a mild dermatitis may occur despite the presence of severe edema (cases 3 and 18). In view of

the other signs usually associated with a typical case of pellagra, we feel justified in regarding as pellagrins the 3 patients in whom the rash was absent (cases 1, 5 and 17). However, in the cases available to us the most frequent manifestations were a large fatty liver, edema of varying severity, dermatitis, angular and labial stomatitis and graying of the hair with varying degrees of alopecia.

**Biochemical Observations**—Because of the difficulties in drawing blood from these emaciated or grossly edematous children it was not possible to conduct full biochemical studies on all the patients recorded here. However, hematologic investigations were conducted in 7 cases. Hemoglobin estimations were made with the Zeiss hemoglobinometer (100 per cent, 16 Gm of hemoglobin per hundred cubic centimeters of blood). Some degree of microcytic anemia was present in all the children examined. The macrocytic anemia described by Trowell was not observed. The white cells showed no abnormality other than a slight leukocytosis with a relative lymphocytosis. Despite the extremely low concentrations of serum proteins encountered in many of the patients, the sedimentation rate (one hour Wintrobe method) was normal.

The serum proteins were in the main reduced, the reduction of the albumin fraction being most noticeable, with a consequent lowering of the albumin-globulin ratio.

In 14 of the 23 cases the stools were large, pale, fermenting, offensive and greasy. In 8 cases the stools were examined biochemically. The results are summarized in the table. In 7 cases the fat content was excessive, consisting of a large amount of split and unsplit fats. In view of Andersen's careful studies<sup>13</sup> it is not possible on the basis of the nature of the fat in the stool to attribute the origin of such a fatty stool either to malabsorption or to pancreatic deficiency. Such fatty stools in infantile pellagra have also been reported by Gillan,<sup>14</sup> Trowell<sup>9b</sup> and Kark.<sup>8a</sup>

#### RESPONSE TO THERAPY

**Vitamin Therapy**—An analysis of the cases of infants with pellagra admitted to the Johannesburg Non-European Hospital during the last

13 Andersen, D. H. Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease. A Clinical and Pathologic Study, *Am J Dis Child* **56** 344 (Aug) 1938, Cystic Fibrosis of Pancreas, Vitamin A Deficiency and Bronchiectasis, *J Pediat* **15** 763 (Dec) 1939.

14 Gillan, R. V. Investigation into Certain Cases of Oedema Occurring Among Kikuyu Children and Adults, *East African M J* **11** 88 (June) 1934.

Symptoms, Treatment and Results in Twenty-Three Cases of Infantile Pellagra

Case Number	Age, Years	Sex	Duration of Illness, Weeks	Diarrhea	Character of Stool	Cheilosis	Angular Stomatitis	Glossitis	Cutaneous Lesions	Edema	Size of Liver	R B C Count	Hemoglobin, per Cent	Sedimentation Rate	Serum Protein			Vasermann Reaction	Stools			Category of Liver Microscopically	Treatment	Result
															Albumin	Globulin	Total Protein		Water Content, per Cent	Total Fat, per Cent	Unsaponifiable Fat, per Cent			
1	2 2/12	F	2	++	G	+	+	+	0	1	1				19	11	30				I	Nicotinic acid and thiamine and vitamin C by injection, brewers' yeast and a halfbut liver oil preparation orally	Died	
2	1 2/12	F	6	++	B	++	+	+	44	44	3				20	19	39				I	Brewers' yeast, orange juice and a halfbut liver oil preparation	Died	
3	1 3/12	F	4	+	F	+	+	-	22	44	0	396	53	3	19	16	35	Neg	83	52	0	II	Nicotinamide, thiamine hydrochloride, vitamin C, all by injection	Died
4	1 3/12	F	4	++	F	++	++	++	32	12	0	42	60	6				Neg	76	51.3	0	II	Full ward diet	Died
5	9/12	M	3	++	F	++	++	++	0	11	0	14	80	4	22	12	34	Neg	86.5	54	32	I	Riboflavin and nicotinamide by injection	Died
6	6/12	F	2	++	G	++	++	0	42	0	1	12	80	12	25	16	41		81	29	15	I	Full ward diet	Died
7	3 6/12	F	3	++	B	++	++	0	41	13	2				18	29	47	Neg				I	Full ward diet	Died
8	1 1/12	F	3	++	B	++	++	0	14	44	2	366	66	11	17	26	43	Neg				I	Liver extract by injection	Died
9	2 1/12	F	3	0	G	++	++	0	13	43	2	32	50	7	20	16	36	Neg				III	Liver extract by injection	Recovered after 24 days
10	1 1/12	M	2	0	G	++	++	0	43	44	2	32	50	7	20	16	36	Neg				III	Liver extract by injection	Recovered after 30 days
11	2 1/12	M	3	+	F	++	++	0	42	44	2	396	53	8	25	11	36	Neg	83	38	25	II	Liver extract by injection	Recovered after 26 days
12	1 6/12	F	3	+	F	++	++	+	23	31	2				21	24	45	Neg				II	Liver extract by injection	Recovered after 35 days
13	4	F	2	+	F	+	+	+	43	44	2				19	19	38	Neg	84	3	29	II	Liver extract by injection	Recovered after 35 days
14	3	M	4	+	G	++	++	+	32	33	2											I	Liver extract by injection	Recovered after 32 days
15	2 2/12	M	3	+	F	++	++	0	44	44	1											III	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 17 days
16	3	F	4	+	F	+	+	0	32	33	2				18	18	36	Neg				II	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 19 days
17	1 6/12	F	1	+	F	+	+	+	0	22	0				14	24	38					II	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 14 days
18	2 4/12	M	3	+	F	+	+	+	11	33	2								80	52	30	I	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 21 days
19	1 7/12	M	4	+	F	+	+	+	32	43	2				20	19	39	Neg	82	21	24	I	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 10 days
20	1 11/12	M	1	+		-	+	+	32	22	0				24	18	42	Neg				II	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 10 days
21	2	F	2	+	F	+	+	0	23	23	2											I	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 10 days
22	2 8/12	M	3	+	F	+	+	+	44	11	2											I	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 14 days
23	1 9/12	M	1	+	F	+	+	+	13	22	2											I	Powdered stomach 10 Gm 5 cc N/10 HCl	Recovered after 18 days

The code for the symbols and figures in the table is as follows

Cutaneous lesions

Extent (first digit in column)

1 = buttocks and genitalia only

2 = buttocks and legs and feet

3 = buttocks and legs and feet and shoulders

4 = buttocks and legs and feet and shoulders and hands

and face

Severity of cutaneous lesions (second digit in column)

0 = dry skin

1 = bronze spots

2 = plaques

3 = desquamation

4 = ulceration

Edema

Extent (first digit in column)

1 = feet and ankles

2 = feet and ankles and genitalia

3 = feet and ankles and genitalia and hands and arms

4 = feet and ankles and genitalia and hands and arms

and face and eyelids

Severity (second digit in column)

1 = just pitting

2 = moderate

3 = gross edema

4 = eyes occluded

Liver

S/c

0 = not palpable

1 = just palpable

2 = below costal margin 2 to 3 fingerbreadths

3 = to umbilicus or below

Microscopic classification

1st category

2d category

3d category

Character of stools

G = green

B = bloody

F = fatty

four years reveals a 40 to 60 per cent mortality<sup>15</sup>—and this despite the administration of both vitamins and a full diet. Our own studies indicate that, no matter how severe the clinical manifestation of the disease, provided the liver is not severely damaged the patients will recover on any form of rational therapy. The greatest difficulty presented by these children is their loss of appetite. Provided they take their feedings they usually recover, albeit slowly. In the presence of severe hepatic damage the response to vitamin therapy is erratic and most unsatisfactory. This is the experience of Youmans and associates<sup>16</sup> and Trowell.<sup>9</sup> It is our impression from the cases recorded here that massive doses of vitamins administered orally or parenterally tend to hasten the progress of the disease. All of the 7 patients treated with vitamins during this study died. In many we observed the desquamation of the skin following the administration of nicotinic acid, but the patients still died. Similar results with nicotinic acid therapy have been recorded by Trowell. Vitamin therapy failed to improve the liver, and, in view of the experimental evidence presented by Handler and Dann<sup>4</sup> in animals and our own observations on human infants, it would appear that the administration of massive doses of nicotinic acid and other crystalline vitamins is contraindicated in cases of severe infantile pellagra.

**Liver Therapy**—Our results with liver therapy were considerably better than those with vitamins. Five of the 7 children lived.

The first sign of recovery was the gradual loss of edema fluid. The child looked brighter after two to three days' therapy, and the appetite improved. After five days' treatment the oral lesions commenced to heal, and the skin started peeling.

The liver improved more slowly than the clinical condition, and even at the end of three to four weeks when the children were discharged as clinically normal, there was a considerable degree of residual liver damage as seen histologically from the biopsy specimen.

In view of the 2 deaths of patients treated with liver extract and of the slow response in those children who recovered, we did not consider that liver therapy was entirely satisfactory.

Several other methods of therapy have been tried. Blood and serum transfusions were of

no avail. One patient, a child of 9, was treated with 150 to 200 Gm of fresh, raw, minced beef pancreas daily. This was administered through a gastric tube. The method is cumbersome and tedious, and, although we persisted with this treatment for two weeks, the response was very slow. The liver underwent considerable improvement during the first ten days but showed no change thereafter despite the continuance of therapy. The edema, too, improved slowly. The response to raw pancreas as seen in this single case was similar in many respects to that obtained with large doses of liver extract administered parenterally.

**Treatment with Powdered Stomach**—In a previous paper we demonstrated that powdered stomach has a remarkable lipotropic action on the fatty livers of infantile pellagrins. Coincident with the rapid disappearance of fat from the liver there was also a remarkable improvement in the clinical picture.

Within twenty-four to forty-eight hours of the exhibition of dried hog's stomach there was a sudden loss of edema fluid. Eyes which were previously occluded by edema opened overnight. The edema of the limbs and genitalia disappeared so rapidly that the children frequently lost between 1 and 3 pounds (454 to 1,307 Gm) in weight in twenty-four to forty-eight hours. The cutaneous and oral lesions healed surprisingly quickly, and within three to four days of the first dose of powdered stomach the skin commenced to desquamate, and within seven to ten days the skin appeared normal. The diarrhea and steatorrhea ceased within two to three days. The children rapidly lost their peevishness and irritability, they regained their appetites and ate well and on clinical grounds could be regarded as cured within ten to fourteen days.

As we have already shown, the livers recovered rapidly and were almost normal when the patients were discharged.

Although powdered stomach was administered for only five days, the improvement continued after therapy was suspended. We feel convinced that had it been possible for us to continue our treatment for a few more days even the small amount of fat remaining in the liver would have been completely removed and recovery might have been even more rapid. In view of our results we have no hesitation in regarding powdered stomach as a life-saving drug in the treatment of severe infantile pellagra. The rapid improvement in the clinical condition and the nervous symptoms as well as the almost immediate loss of edema fluid and the cessation of

<sup>15</sup> Gillman, T. Diet and Disease in Bantu Children, South African J. M. Sc., to be published.

<sup>16</sup> Youmans, J. B., Bell, A., Donley, D., and Frank, H. Endemic Nutritional Edema. Serum Proteins and Nitrogen Balance, Arch. Int. Med. 51:45 (Jan) 1933.

the diarrhea and steatorrhea move us to suggest that powdered stomach may be of considerable value in the treatment of allied diseases in infants, especially celiac disease and other steatorrheas, nutritional edemas, infantile atrophy and pink disease. Our reasons for this opinion will become patent from the following comment.

## COMMENT

The syndrome of infantile pellagra described by Trowell and later by Kark and confirmed by our own study is widely prevalent in Africa.<sup>17</sup> There are several other diseases of unknown cause in which many of the features are indistinguishable from those seen in infantile pellagra. The most striking in children are celiac disease,<sup>18</sup> infantile atrophy,<sup>19</sup> cystic fibrosis of the pancreas,<sup>13</sup> and nutritional or wari edema.<sup>20</sup> Among adults, sprue and idiopathic steatorrhea<sup>21</sup> are also characterized by bulky fatty stools, edema and post mortem, by a fatty liver.

Although the causes of all these diseases are unknown, the diseases have one feature in common—they all improve to a variable extent after treatment with liver extract.<sup>22</sup> In recent years it has been suggested that a nutritional imbalance is directly or indirectly responsible for the initiation of these diseases.<sup>23</sup>

The evidence available leaves little doubt that infantile pellagra is an expression of severe malnutrition. This disease may become manifest soon after the children are weaned and can be related to the inadequate diet. However, once the disease is established it responds erratically to dietary treatment. The failure of vitamin

therapy of this disease is being recognized by an increasing number of investigators.<sup>24</sup> From our careful study of the reactions of the liver during therapy with vitamins, liver and powdered stomach, we are led to conclude that, although this disease is initiated by a dietary imbalance secondary pathologic changes soon supervene and the disease can no longer be alleviated by a full diet and vitamin concentrates. The mental symptoms, cutaneous lesions, glossitis, anemia, edema and steatorrhea are in our opinion immediately related, not to the initial malnutrition, but to the secondary pathologic processes resulting from attempts by the organism to readjust its metabolism to the deficient diet.

We have already adduced cogent evidence to substantiate this opinion from our analysis of the response of the fatty liver to therapy.<sup>2</sup> This view is strengthened by a critical analysis of the origin of the edema and steatorrhea and their disappearance after the administration of powdered stomach.

The cause of the extensive edema in infantile pellagra, celiac disease, infantile atrophy, nutritional edema, sprue and cystic fibrosis of the pancreas has been the center of much controversy. Some investigators regard this edema as resulting from severe protein deficiency,<sup>25</sup> while others consider it to be a manifestation of beriberi.<sup>26</sup>

It is known that low serum protein levels may be attended by edema.<sup>27</sup> In infantile pellagra, although the serum proteins are often reduced, the extent of this reduction by no means bears any relation to the extent or the severity of the edema. In case 1, with a total serum protein content of 3 Gm per hundred cubic centimeters there was only a mild edema of the feet and ankles. In case 9, on the other hand, there was an extensive edema of both upper and lower extremities, and the eyes were completely closed by the edematous eyelids. The total serum pro-

<sup>17</sup> Kark and Trowell.<sup>2</sup>

<sup>18</sup> (a) Parsons, L. G. Celiac Disease, *Am J Dis Child* **43** 1293 (May) 1932, (b) Coeliac Disease, in Parsons, L. G., and Barling, S. *Diseases of Infancy and Childhood*, London, Oxford University Press, 1933, vol 1, p 363.

<sup>19</sup> Maitland-Jones, A. Infantile Atrophy, in Parsons, L. G. and Barling, S. *Diseases of Infancy and Childhood*, London, Oxford University Press, 1933, vol 1, p 363.

<sup>20</sup> (a) Waring, J. I. Nutritional Heart Disease in Children, *Am J Dis Child* **55** 750 (April) 1938, (b) Gounelle, H., Marche, J., and Bachet, M. The Blood Protein in Famine Oedema, *Nutrition Abstr & Rev* **12** 611 (April) 1943.

<sup>21</sup> (a) Manson-Bahr, P. *The Dysenteric Disorders*, ed 2, London, Cassell & Company, Ltd, 1943, (b) Molina, R. R. Sprue in Puerto Rico. A Clinical Study of One Hundred Cases, *Puerto Rico J Pub Health & Trop Med* **17** 134 (Dec) 1941, (c) Sprue in Porto Rico—Ten Years Later, *ibid* **18** 314 (March) 1943.

<sup>22</sup> Parsons<sup>18b</sup> Maitland-Jones<sup>19</sup> Manson-Bahr<sup>21a</sup> Hamilton-Fairley, N. Tropical Sprue, in Rolleston, H. *British Encyclopaedia of Medical Practice*, London, Butterworth & Co, Ltd, 1939, vol 11, p 419.

<sup>23</sup> Parsons<sup>18b</sup> Manson-Bahr<sup>21a</sup>

<sup>24</sup> Trowell<sup>2a</sup> Youmans, Bell, Donley and Frank<sup>16</sup> Normet, L. Report on the Pathogenesis of the Oedema of Annam and Deficiency Diseases, *Bull Acad de med, Paris* **117** 239 (Feb) 1937.

<sup>25</sup> Liu, S. H., Chu, H. I., Wang, S. H., and Chung, H. L. Nutritional Edema, *Chinese J Physiol* **6** 73 (Feb 15) 1932, cited by Trowell<sup>2a</sup>.

<sup>26</sup> Wheeler, G., in discussion on Youmans, J. B. Endemic Nutritional Edema in Tennessee. Public Health Problem, *South M J* **26** 713 (Aug) 1933.

<sup>27</sup> Weech, A. A., and Ling, S. M. Relation of Serum Proteins to Occurrence of Nutritional Edema, and to the Effect of Inorganic Salts, *J Clin Investigation* **10** 869 (Oct) 1931. Lepore, M. J. Edema Produced by Plasma Protein Depletion (Plasmapheresis), *Arch Int Med* **50** 488 (Sept) 1932.

tein content in this patient (47 Gm per hundred cubic centimeters) was almost within the lower limits of normality, the albumin moiety being almost identical with that in case 1. This lack of correlation between the level of the serum proteins and the severity of the edema in malnutrition substantiates the views of Youmans and associates<sup>16</sup> and of Gounelle, Marche and Bachet<sup>20b</sup>.

It is known that the liver plays an important direct role in water metabolism quite apart from its effects on serum protein<sup>28</sup>. Selye, Collip and Thomson,<sup>29</sup> in a series of carefully planned experiments, have shown that intravenous injection of isotonic solution of sodium chloride into partially hepatectomized rats leads to the development of a diffuse edema associated with the accumulation of fat in the residual portion of the liver. If a venesection is performed on these partially hepatectomized animals that have been given transfusions, the edema can be prevented, although some fat still appears in the liver. Moreover, they demonstrated that partial hepatectomy inhibits the diuresis which invariably followed the transfusion of saline solution in normal animals. It follows from these experiments that the administration of fluids to animals with hepatic insufficiency leads to visible disturbances in the surviving portions of the liver and impairment of renal function associated with severe edema. These experiments indicate that the liver is directly concerned in water metabolism and that the disturbances in water metabolism in hepatic disease may in themselves aggravate the initial lesion in the liver.

This evidence from experimental work in animals as well as our observations on children suffering from infantile pellagra throws new light on the cause of the edema in malnutrition.

We have established in our previous study that the liver in infantile pellagra can be almost avascular. The sinusoidal bed is virtually occluded, the portal veins are small, and it was with the greatest difficulty that we were able to identify even the largest radicles of the hepatic vein. Judging from the degree of avascularity, it appeared in many instances as if the infant were almost hepatectomized. The vascular bed

of the normal liver is enormous. In preliminary experiments which we have conducted with adult livers we have demonstrated that the large hepatic veins are capable of holding at least 500 cc of fluid. Moreover, by injectional methods we have established that the vascular bed of the normal adult human liver may, without distention, accommodate over 800 cc of fluid. When the vascular bed of the liver becomes occluded, as in infantile pellagra, the volume of blood which would normally be contained in hepatic vessels must now be displaced into the systemic circulation. This addition to the circulating blood volume in the absence of normal renal function probably contributes to the displacement of fluid into the tissues.

Jones and Eaton<sup>30</sup> have recorded the occurrence of a diuresis which precedes by several days other signs of recovery from hepatic disease. Under treatment with powdered stomach the liver of an infantile pellagrin improves in a remarkable fashion.<sup>2</sup> This improvement is associated with a rapid diminution in the edema resulting from a diuresis, which may lead to loss of 20 ounces (566 Gm) of body weight in forty-eight hours. The rapid diuresis which heralds the sudden recovery of patients treated with powdered stomach suggests that the improvement in the liver is associated with the reestablishment of conditions conducive to renal function. In view of all this evidence there seems little doubt that the edema in infantile pellagra is intimately related in an inexplicable fashion to the extensive hepatic damage which we have demonstrated to be a constant feature in this disease.

The rapid subsidence of the edema with treatment with powdered stomach indicates that the stomach too, in some way, plays an important part in water metabolism. Petri and associates<sup>31</sup> noted the occurrence of edema in gastrectomized young swine. Since the stomach is almost invariably implicated to a greater or lesser extent in pellagra<sup>32</sup> and since, as we shall see later

30 Jones, C. M., and Eaton, F. B. The Prognostic Significance of Spontaneous Diuresis in Acute and Subacute Disease of the Liver, *New England J Med* **213** 907 (Nov 7) 1935.

31 Petri, S., Norgaard, F., and Bing, J. Pathological Changes Produced by Gastrectomy in Young Swine, *Am J M Sc* **195** 717 (June) 1938.

32 (a) Flinker, R. The Function of the Stomach in Pellagra, *Arch f Verdauungskr* **57** 282 (May) 1935. (b) Rubio, D. M. Studies in Pellagra. I. The Gastric Secretion, *Trop Dis Bull* **40** 79 (Jan) 1943. (c) Gillman, T. Critical Evaluation of Neutral Red Excretion and Acid Secretion Tests of Gastric Function in the Normal and in Subjects with Gastric Disorders, *Gastroenterology* **3** 188 (Sept) 1944.

28 Adolph, E. F., Gerbas, M. J., and Lepore, M. J. Redistribution of Water Following Transfusions and Infusions, *Am J Physiol* **107** 647 (March) 1934. Randall, L. A., and Roberts, G. M. Increased Water Exchange Following Eck Fistula in Dogs, *ibid* **117** 48 (Oct) 1936.

29 Selye, H., Collip, J. B., and Thomson, D. L. Some Interrelations Between Water and Fat Metabolism. Relation to Disturbed Liver Function, *Lancet* **2** 297 (Aug 10) 1935.

the interference with gastric function may modify the course of infantile pellagra and other diseases, the importance of this organ in the maintenance of normal water metabolism and the role of gastric dysfunction in the production of edema cannot be overlooked

From the foregoing it is apparent that there is an intimate interrelationship between the stomach, the liver and the kidney in the maintenance of normal water metabolism. The fact that edema is a much more constant feature in infants than in adults suffering from pellagra implies that the mechanism regulating water metabolism is more sensitive in children than in adults. McCarrison<sup>33</sup> has shown that young animals are much more liable to edema when malnourished than adults on the same diet. In this connection it is noteworthy that it is much more difficult to induce damage to the liver with mealie pap and sour milk in old than in young rats,<sup>34</sup> and our aspiration biopsy studies of pellagrins have revealed a notable difference in the nature and severity of the pathologic process in the livers of adults as compared with those of children.<sup>35</sup>

Another feature of infantile pellagra is the frequent occurrence of steatorrhea. The appearance of large quantities of split and unsplit fat in the stools is common to a number of other diseases. The factors responsible for steatorrhea are still unsettled.

In a series of excellent reviews Parsons has repeatedly emphasized that "the probable explanation of celiac disease lies in a change of physico-chemical nature in the absorptive mechanism of the intestine"<sup>18a</sup>. This view has recently been reaffirmed both for celiac disease and for sprue<sup>36</sup>. The flat blood fat curves repeatedly recorded for patients with these diseases<sup>37</sup> may, in our opinion, be as easily accounted for by an increased tolerance for fat as by a deficient absorption of it. Moreover, the fat balance curves published by Parsons<sup>18a</sup> indicate that patients suffering from celiac

disease are capable of absorbing considerable amounts of fat. However, both in celiac disease and in sprue signs of vitamin deficiency as well as edema frequently become manifest. Tetany, commonly observed in celiac disease, has also been described by Drewe in malnourished African children suffering from steatorrhea<sup>38</sup>. Parsons concluded that whether or not the disease is initiated by avitaminosis "there can be no shadow of doubt that a defect, not in supply, but in the absorption of vitamins resulting from the impaired alimentary absorption is the cause of many of the most characteristic symptoms of the disorder".

Blackfan and Wolbach<sup>39</sup> have described the occurrence in children of fatty livers and cystic fibrosis of the pancreas in association with evidence of vitamin A deficiency. Later Andersen reported similar changes in infants and children<sup>13</sup>. She emphasized the invariable association of cystic fibrosis of the pancreas and was undecided as to whether the primary cause of the steatorrhea was a vitamin deficiency or the pancreatic lesions.

Judging from clinical and experimental evidence, we are of the opinion that steatorrhea can be initiated by a dietary imbalance and is not necessarily due to a disturbance in absorption of fat. Experimentally we have demonstrated that rats fed on mealie pap and sour milk commonly have cystic changes of the pancreas similar to those described and portrayed by Andersen in children<sup>13</sup>. In our dietary experiments the rats also were found to have fatty livers<sup>34a</sup>. Whereas Andersen was unable in her human subjects to ascertain the sequential relations between the fatty liver and the pancreatic lesion, we can state with assurance<sup>34b</sup> that in rats the fatty liver precedes by many months the cystic changes in the pancreas<sup>40</sup>.

Clinically there seems little doubt that infantile pellagra is directly attributable to malnutrition. From our careful analysis of the diets of our patients, as well as those reported in Trowell's series, it is clear that the fat content of the diets is extremely low and is insufficient to account for the large quantities of fat excreted in the feces. In these circumstances the steatorrhea in infantile pellagra can be accounted for only by an increased excretion of fat. In a

38 Drewe, F. Personal communication to the authors.

39 Blackfan, K. D., and Wolbach, S. B. Vitamin A Deficiency in Infants. A Clinical and Pathological Study, *J. Pediat.* **3**:679 (Nov.) 1933.

40 In a single fatal case of severe malnutrition recently observed, the pancreas showed the early development of cystic changes such as we have seen in our rats. The liver in this patient was grossly fatty.

33 McCarrison, R. *Studies in Deficiency Disease*, London, H. Frowde, 1921.

34 (a) Gillman, J., Gillman, T., Gilbert, C., and Mandelstam, J. The Production of Severe Hepatic Injury in Rats by Prolonged Feeding of Maize-Meal Porridge (Mealie-Pap) and Sour Milk, to be published. (b) Gilbert, C., and Gillman, J. Diet and Disease in the Bantu, *Science* **99**:398 (May 19) 1944.

35 Gillman, J., and Gillman, T. Liver in Pellagra, *Lancet* **2**:161 (July 29) 1944, footnote 2.

36 Stannus, H. S. Sprue, *Tr. Roy. Soc. Trop. Med. & Hyg.* **36**:123 (Nov.) 1942.

37 Parsons<sup>18a</sup>. Adlersberg, D., and Sobotka, H. Fat and Vitamin A Absorption in Sprue and Jejuno-ileitis, *Gastroenterology* **1**:357 (April) 1943.

previous study<sup>2</sup> we have suggested that the accumulation of fat in the liver and its excretion in the stool, associated with extreme emaciation, are an expression of the conversion of carbohydrate into fat together with an inability of the tissues to utilize this fat

Thus, although infantile pellagra is initiated by a dietary imbalance, once the disease has progressed to the stage where the fatty liver, steatorrhea, edema and dermatitis become manifest, then vitamins fail to improve the conditions of a large proportion of the patients. The failure of vitamins, even when administered parenterally, indicates that the factor of absorption is unimportant. The organism is apparently incapable of utilizing vitamins even when made available in large concentrations by parenteral routes. But, even when vitamins are said not to be absorbed from the alimentary tract, powdered stomach administered orally is able within two to three days to produce such a profound readjustment in the metabolism of the diseased organism that the diet and vitamins can be effectively utilized.

Whereas in infantile pellagra dietary imbalances lead to the development of steatorrhea, this steatorrhea in infantile pellagra, as in celiac disease, may in turn be responsible for an intensification of the severity of the disease, as expressed by disturbed gastric function, macrocytic anemia and edema. This intensification of the clinical picture is probably attributable not so much to the malabsorption of essential dietary factors as to the hitherto unappreciated subtle changes produced by the continuous presence of fat in the alimentary tract.

It has been known for a long time that neutral fat inhibits gastric secretion as well as gastric motility. This inhibition results from the contact of neutral fat with the mucous membrane of the duodenum, jejunum and large bowel. By a series of carefully planned experiments<sup>41</sup> a hormone (enterogastrone) said to be responsible for the inhibition of gastric function resulting from the ingestion of fat was isolated. It is

not inconceivable that the continuous presence of fat in the alimentary tract in infantile pellagra may lead to the liberation of enterogastrone. This hormone, in turn, contributes to the partial or complete suppression of gastric function. We have already indicated that the stomach, together with the liver and the kidney, is intimately concerned with water metabolism. Any interference with this delicate mechanism might result in the production of edema.

It is generally known that the stomach, through its intrinsic factor, influences hemopoiesis. The chronic inhibition of gastric function by the continuous liberation of enterogastrone in steatorrhea might so disturb the gastrohepatic relationship as to lead to the macrocytic or microcytic anemia so frequently observed in infantile pellagra.<sup>9</sup> Moreover, the apathy, atonia and anorexia, manifestations of severe malnutrition, can also be explained by an impairment of gastric function.

Distention of the bowel is known to produce profound effects on hepatic function.<sup>42</sup> The pronounced distention of the intestinal tract in steatorrheas cannot be overlooked in the light of its possibly deleterious effects on the functions of the liver.

That infantile pellagrins do not respond to vitamins but respond dramatically to powdered stomach strongly suggests that the latter preparation supplies an essential substance normally elaborated by the stomach, which breaks the vicious circle, facilitating in this way the recovery of the patient.

The similarities between infantile pellagra and other conditions in which steatorrhea, edema, cutaneous lesions, anemia, anorexia and fatty changes in the liver occur suggest a disturbance in the same underlying mechanism. Whether the initiating factor is the same in all these diseases remains to be determined. Nevertheless, during their evolution a disturbance of fat metabolism eventually occurs. Once this disturbance becomes manifest, all these diseases seem to follow a common course in their subsequent evolution.

The stages in the emergence of the signs and symptoms associated with sprue have been graphically described by Manson-Bahr. Dyspepsia, followed by the typical gastrointestinal disturbances, precedes by months the onset of the anemia.<sup>21</sup> As in infantile pellagra, so in

42 Schnedorf, J. G., and Orr, T. G. The Effect of Small Intestine Distention upon the Bile and Urine Flow. Its Possible Relationship to the Hepato-Renal Syndrome, *Am J Digest Dis* 8:303 (Aug) 1941.

41 Feng, T. P., Hou, H. C., and Lim, R. K. S. Mechanism of the Inhibition of Gastric Secretion by Fat, *Chinese J Physiol* 3:371 (Oct) 1929. Kosaka, T., Lim, R. K. S., Ling, S. M., and Liu, A. C. On the Mechanism of the Inhibition of Gastric Secretion by Fat. A Gastric-Inhibitory Agent Obtained from the Intestinal Mucosa, *ibid* 6:107 (Feb 15) 1932. Ivy, A. C., and Gray, J. S. Enterogastrone, in *Cold Spring Harbor Symposia on Quantitative Biology*, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol 5, p 405. Babkin, B. P. Secretory Mechanism of the Digestive Glands, New York, Paul B. Hoeber, Inc., 1944.

sprue, the presence of fat in the intestine probably induces the formation of enterogastrone, which in turn inhibits gastric activity. Judging from the length of time by which the steatorrhea precedes the onset of the anemia in sprue, the inhibition of gastric function probably continues for several months.

Castle and others,<sup>43</sup> from their thorough study of sprue, concluded that the macrocytic anemia in this disease is attributable to the inhibition of the formation of the intrinsic factor. However, Molina demonstrated the presence of free hydrochloric acid in 82 of 100 patients with sprue examined. If, as we have suggested, enterogastrone is responsible for the inhibition of the function of the stomach in steatorrhea, it would appear at first difficult to account for the dissociation of the activities of the gastric mucosa.

The stomach is known to have at least three different types of function, they are the formation of gastric juice, the production of the intrinsic factor and the excretion of various substances, including injected neutral red. There can be dissociation of the secretory activities of the stomach.<sup>44</sup> In cases of pellagra, for example, free acid may continue to be formed even though the stomach is unable to excrete neutral red, and vice versa. Moreover, in a single classic case of tropical sprue Dr Foy and Dr Kondi kindly afforded us the opportunity of testing the excretory function of the stomach with neutral red. The macrocytic anemia in this patient, on the basis of Castle's finding, was strong evidence of an impairment in the formation of the intrinsic factor. The excretory function of the stomach was also impaired, but free acid was secreted after histamine had been injected. Thus in this case the secretion of free acid was not grossly impaired, but there was a delay in the excretion of neutral red, and the intrinsic factor was lacking. It is not unlikely, therefore, that enterogastrone may cause a differential inhibition of gastric function resulting in suppression either of the formation of the intrinsic factor as in sprue or of the secretion of hydrochloric acid as in some cases of pellagra. Prolonged inhibition, as in chronic sprue, may eventually result in complete suppression of all

the functional activities of the stomach. Once the steatorrhea is fully established, the disease changes its character, and then the edema, emaciation, anorexia and fatty liver develop as in infantile pellagra.

Since this analysis of the evolution of sprue and infantile pellagra is applicable to other diseases in which steatorrhea is a dominating feature, and in view of the beneficial but not entirely satisfactory results achieved with crude liver extracts, it is justifiable to suggest that powdered stomach, so successful in infantile pellagra, be substituted for or administered with crude liver extract in the treatment of steatorrhea.

Despite the close relationship known to exist between the stomach and the liver, it is interesting that much greater importance should have been attached to liver extracts than to the principles isolated from the stomach only three years later. Powdered stomach has a remarkable lipotropic effect on the liver, restores the gastro-hepatorenal relationship (as evidenced by the removal of the edema), benefits the nervous and hemopoietic systems in anemias and facilitates the utilization of essential food substances with consequent suppression of steatorrhea in a severely damaged organism. All these important effects indicate the necessity for an assessment of the active principles of the stomach and of their relation to the active principles of the liver in the bodily functions connected with steatorrhea.

Finally, a significant thesis emerges from this and other of our studies, namely, that a disease at a certain stage loses its connection with the initial cause. The subsequent course of the disease may then be determined by the secondary pathologic changes. Once the disease manifests its altered character, our efforts to break the vicious spiral should then be directed toward the mainspring responsible for maintaining the disease process and for interfering with the harmonious integration of bodily activities. This approach may stimulate and direct the search for new forms of therapy for those diseases which hitherto have proved refractory to the present methods of treatment.

#### SUMMARY

From a study of 23 cases of pellagra in infants and children it was demonstrated that the main clinical findings were a varying degree of edema, dermatitis, angular and labial stomatitis (cheilosis), graying of the hair with varying degrees of alopecia, steatorrhea and a large fatty liver.

43 Castle, W. B., and others. Etiology and Treatment of Sprue, *Arch Int Med* 56:627 (Oct) 1935.

44 Gillman, T. Excretion of Neutral Red by the Gastric Mucosa, A Valuable Test of Gastric Function, *South African J. M. Sc.* 8:50 (Feb) 1943, footnote 32c. Solovey, E. G. Excretory Function of the Stomach, Dissert., Moscow, 1938, cited by Lourja, R. A. The Excretory Function of the Stomach and Its Clinical Role, *Acta med. U. R. S. S.* 2:310, 1939.

Histologic examination of fragments of liver obtained by aspiration biopsy on the day of the patient's admission revealed the presence of a greater or lesser amount of fat in the liver cells. The fatty change in the liver was found to be a constant feature of infantile pellagra, and it was not due to intercurrent infection as was previously believed. The degree of accumulation of fat in the liver proved to be a much more accurate measure for predicting the outcome of each case than the clinical findings. No aspiration biopsies were essential in controlling therapy, for it was found that in cases with great accumulation of fat in the liver vitamins together with a full diet appeared to aggravate the condition. All the patients in this series treated with vitamins died. Liver extract and especially powdered stomach depleted the fat from the liver, and this depletion in turn was invariably associated with a dramatic improvement in the condition of the patient.

Powdered stomach has a vigorous lipotropic action in infantile pellagra. Five days' treatment with 10 Gm a day was adequate to allow for a continued depletion of fat from the liver even after treatment was suspended. A study of the reactions of the liver during therapy with vitamins, liver extract and powdered stomach led to the conclusion that, although infantile pellagra is initiated by dietary imbalance, the secondary pathologic changes which supervene cannot be alleviated by a full diet and vitamin concentrates.

The edema of infantile pellagra is not related to the level of the serum proteins. It was suggested that, at least in infants, the normal

water metabolism is dependent on a subtle but intimate interrelationship of the stomach, liver and kidneys. The edema in infantile pellagra probably results from a disturbance of this gastro-hepatorenal mechanism.

In view of the low fat content of the diet, the steatorrhea in infantile pellagrins was regarded as resulting not from malabsorption of fat but rather from an increased excretion of fat into the bowel. It was concluded that in infantile pellagra carbohydrate is converted into fat which cannot be utilized. The evidence available indicates that fat continuously present in the bowel liberates enterogastrone, which in turn inhibits gastric function. It is suggested that this chronic inhibition of gastric function with the consequent disturbance in the gastrohepatic relationship could lead to the macrocytic or microcytic anemia, nervous symptoms and edema so commonly associated with steatorrhea.

The similarities between infantile pellagra and other conditions in which steatorrhea appears early in the disease process strongly suggest that once the disturbance in fat metabolism has occurred, irrespective of the initiating cause, all these diseases follow a common course in their later evolution.

In view of the rapid cessation of the steatorrhea and the accompanying general improvement in infantile pellagrins treated with powdered stomach, it is recommended that this treatment be given universal trial for other diseases in which steatorrhea is a prominent feature.

Prof. Raymond A. Dart gave suggestions for this study. Miss Winifred Till and Mr. Sidney Dry gave technical assistance.

# COLD HEMAGGLUTINATION IN PRIMARY ATYPICAL PNEUMONIA AND OTHER COMMON INFECTIONS

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Recent reports indicate that large amounts of a cold hemagglutinin appear frequently in the blood of patients with primary atypical pneumonia<sup>1</sup> Apparently, this is not true of patients with other common infections of the respiratory tract, such as pneumococcic pneumonia, the common cold, influenza and pulmonary tuberculosis<sup>2</sup> In view of the simplicity of the titration of cold agglutinin in the serum, this procedure promises to be of value as a practical aid in the differentiation of primary atypical pneumonia from the other common types of pneumonia This differentiation is often difficult, since no clinical or laboratory finding is characteristic of the former syndrome<sup>3</sup>

During the winter and spring of 1943-1944, we studied the phenomenon of cold hemagglutination in 115 patients with pneumonia, in 257 patients with other infections and in 100 normal hospital personnel This was done to evaluate further the specificity and significance of high titers of cold agglutinin in persons with primary atypical pneumonia and to determine whether this serologic test is of any use in the detection of

the carrier state and of certain minor infections of the respiratory tract with the agent (or agents) causing this syndrome The following is a report of our observations on the 472 subjects studied

## NATURE OF COLD HEMAGGLUTINATION

The phenomenon of cold hemagglutination dealt with in this study is due to the action of "a non-specific agglutinin capable of producing clumping of human erythrocytes, irrespective of blood group and usually of certain other heterologous erythrocytes"<sup>4</sup> Although activity is greatest at 0 to 5 C and disappears at 37 C, the range of temperature in which hemagglutination occurs seems to widen as the concentration of the agglutinin increases Apparently, the erythrocytes used in the demonstration of this phenomenon are of fundamental importance, since irregular variations occur in the agglutinability of cells of the various homologous blood groups and of heterologous red blood cells (1 e rabbit, sheep, etc)<sup>1b</sup>

Cold hemagglutinin has been commonly found in normal serums and has been detected in large amounts in serums of persons with a great variety of diseases, particularly trypanosomiasis, hematologic disorders, hepatic cirrhosis and, as already indicated, primary atypical pneumonia<sup>5</sup> The general significance of its presence is unknown There is some evidence that cold hemagglutinin is an immune body, closely related to serum globulin For a detailed review of the general subject of cold hemagglutination, the recent article by Stats and Wassermann should be consulted<sup>5</sup>

## METHODS

Titration of the cold hemagglutinin content of the specimens of serum were carried out by the following method Five cubic centimeters of blood was obtained by venipuncture with use of dry syringe and placed in a clean dry test tube The clot was separated at room temperature by rimming, and the sample was

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1 (a) Peterson, O L, Ham, T H, and Finland, M Cold Agglutinins (Auto-Hemagglutinins) in Primary Atypical Pneumonias, *Science* **97** 167, 1943 (b) Turner, J C, Nisnewitz, S, Jackson, E B, and Berney, R Relation of Cold Agglutinins to Atypical Pneumonia, *Lancet* **1** 765, 1943 (c) Horstmann, D M, and Tatlock, H Cold Agglutinins A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, *J A M A* **122** 369 (June 5) 1943 (d) Meiklejohn, G The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, *Proc Soc Exper Biol & Med* **54** 181, 1943

2 Siffert, R S, and Krautman, B Cold Hemagglutination Reactions in Tuberculosis, *J Lab & Clin Med* **29** 270, 1944 Turner and others<sup>1b</sup> Horstmann and Tatlock<sup>1c</sup> Meiklejohn<sup>1d</sup>

3 Dingle, J H, and Finland, M Virus Pneumonias II Primary Atypical Pneumonias of Unknown Etiology, *New England J Med* **227** 378, 1942

4 Wiener, A S Blood Groups and Transfusion ed 2, Springfield, Ill, Charles C Thomas, Publisher 1939, p 35

5 Stats, D, and Wassermann, L R Cold Hemagglutination—An Interpretative Review, *Medicine* **22** 363, 1943

centrifuged for about ten minutes. The serum was pipetted off into a clean test tube. After serum had been taken for the test, the remainder was stored without preservative at 5 C. No serum was stored in the refrigerator unless it had been removed from the clot, since absorption of hemagglutinin occurs at low temperatures.

Serial dilutions were made of 0.1 cc of the serum in isotonic solution of sodium chloride in small test tubes. The 0.1 cc of serum was added to 0.9 cc of saline solution in the first tube, and 0.5 cc of the resultant mixture was added to 0.5 cc of isotonic saline solution in the second tube and so on. A tube containing only 0.5 cc of saline solution was kept as a control. To each 0.5 cc of the diluted serum and to the control, 0.2 cc of a 2 per cent suspension of thrice washed group O erythrocytes was added, making final dilutions of 1/14, 1/28, 1/56, etc. The tubes were then shaken and refrigerated at 5 C for sixteen to twenty hours.

To eliminate unnecessarily long series of dilutions with serums containing little or no cold agglutinin, a test consisting of three dilutions (1/14, 1/28, 1/56) was set up first. If the titer reached 1/56, a second series of dilutions, from 1/14 to 1/3,584, was set up. Titers in excess of 1/3,584 were determined with a third series of dilutions.

The end point of the titration was the highest dilution in which hemagglutination was detectable microscopically after vigorous shaking to resuspend the sedimented erythrocytes. After the last dilution in which macroscopic agglutination was apparent had been noted, the cells in subsequent tubes were observed directly with the low power objective of the microscope, daylight being used as the source of illumination. At the end point, only a slight amount of hemagglutination was present, as indicated by occasional aggregates of 3 to 5 erythrocytes. In the absence of macroscopic clumping, successive tubes were examined microscopically until a perfectly smooth suspension of red cells was apparent. The control suspension of red blood cells in isotonic solution of sodium chloride failed to reveal agglutinated (or adherent) red blood cells under the described conditions.

The readings were performed quickly at room temperature. Moisture condensing on the cold test tubes was removed by wiping with a clean towel. If cold agglutination was observed, the cell suspensions were incubated at 37 C for one to two hours to allow the disappearance of the agglutination, in order to exclude agglutinins active at this temperature.

A high titer of cold agglutinin was indicated by the formation of solid disks of cells in the low dilutions. Such disks were fragmented into coarse clumps by shaking. With moderately increased titers, the disks were easily broken up into finely granular clumps. Low titers (up to 1/28) were often discernible only with the aid of a concave mirror or with the microscope.

Using this method, we found that the end point of the titration varied with the magnification used in reading it and with the time of refrigeration (table 1). Microscopic agglutination was usually present in one or two dilutions higher than the last one in which it was detectable grossly. Moreover, readings at the end of three hours were one or two dilutions lower than those obtained in sixteen to twenty hours. Apparently the prolonged periods of sedimentation of the cells in the cold increased their tendency to aggluti-

nate (table 1). It will be noted in the presentation of our results that the titers of cold hemagglutinin obtained by us in normal controls and in patients with certain infectious diseases are somewhat higher than those reported elsewhere.<sup>6</sup> It is our belief that these differences are in all likelihood due to variations in method.

The 2 per cent suspension of human group O cells was prepared about every forty-eight hours from citrated blood obtained from a small group of donors and stored at 5 C. The suspensions were made from a stock sample of blood kept at 5 C for periods up to four days. This precaution was taken because of the reported observation that red cells exposed to saline solution rapidly lose their agglutinability while those in contact with plasma do not.<sup>6</sup> However, we were unable to detect any significant alteration in the agglutinability of suspensions of red cells used as long as

TABLE 1—Effects of Magnification and Refrigeration Time on the End Points of Cold Agglutinin Titrations of Human Serum

Serum	Refrigeration for 3 Hours		Refrigeration for 20 Hours	
	Macroscopic	Microscopic	Macroscopic	Microscopic
1	1/224	1/448	1/448	1/1792
2	1/56	1/112	1/112	1/448
3	0	1/14	0	1/14
4	1/56	1/112	1/112	1/448
5	0	1/28	0	1/28
6	1/14	1/56	1/28	1/112
7	1/112	1/448	1/224	1/896
8	0	0	1/14	1/28
9	1/14	1/28	1/28	1/112
10	0	1/28	1/14	1/56
11	0	0	0	0
12	0	0	0	0

ninety-six hours after preparation. The blood used in preparing the suspensions was warmed to room temperature, and the cells were washed three times in 10 volumes of isotonic solution of sodium chloride.

In this study, no attempt was made to detect cold agglutinins in dilutions below 1/14. No effort was made to note the agglutinability of the subject's own cells by his serum in the cold (autoagglutination).

MATERIAL

The normal subjects were hospital personnel who came into contact with patients while working in the hospital wards. Each was questioned prior to the test concerning the occurrence of a recent acute infection of the upper respiratory tract or other illness (within six months), especially pneumonia, chronic cough, mumps, measles, scarlet fever, malaria or jaundice. It was assumed that some of these persons had been exposed to primary atypical pneumonia, since the disease was a common one in the hospital and was encountered from time to time in the hospital personnel. Only 1 titration was done for each normal subject.

The clinical and laboratory data for the patients studied were reviewed, and those for whom the diagnoses were reasonably well established were included in the series (table 2).

A diagnosis of primary atypical pneumonia seemed warranted for 91, or 79 per cent, of 115 patients with pneumonia. In selecting this group, we were guided by

6 Footnotes 2 and 4

the diagnostic criteria outlined in recent articles,<sup>7</sup> particularly the mode of onset, the clinical course, the results of physical examination, the roentgenographic findings, the results of culture of sputum when done and the type of responses to sulfonamide drugs when given. Since none of these criteria are specific, differential diagnosis was often difficult.

In the 24 other patients with pneumonia, the disease seemed to be of bacterial origin. There were 8 with lobar pneumonia or bronchopneumonia due to pneumococci (types 1, 2, 4, 5, 7, 12), in 1 the disease was attributed to the beta hemolytic *Streptococcus* and in 1 to *Staphylococcus aureus*. For 14 others, although no pathogenic bacteria were found in the sputum, the findings suggested lobar pneumonia or bronchopneumonia caused by bacteria. In 5 of these 24 patients, the disease was complicated by empyema or pleural effusion.

On the other hand, in several cases of primary atypical pneumonia in which streptococci (alpha or beta hemolytic) were found in the sputum, the organisms were regarded as the usual flora seen in the

For persons with other infectious diseases, many of the determinations of cold agglutinin were single observations made at varying times after the onset of the disease. In some instances, especially for patients with measles and scarlet fever, determinations were made at the height of the disease and two or three weeks later.

The group classified as having minor infections of the respiratory tract included patients with acute catarrhal fever, acute pharyngitis, acute tonsillitis, influenza and acute tracheobronchitis. Infections of this type have been observed during epidemics of primary atypical pneumonia.<sup>7c</sup> The patients with a diagnosis of influenza were seen during an epidemic caused by type A influenza virus in December 1943 and January 1944. In general, the illnesses in this group were of short duration, and repeated observations of the cold hemagglutinin titer during convalescence were not often possible. However, the late influence of such illnesses on the cold hemagglutinin titer was studied in some of the normal hospital personnel, as indicated subsequently.

TABLE 2—Distribution of Cold Hemagglutinin Titers in 472 Subjects

Clinical Group	Sub- jects	Tests	Cold Hemagglutinin Titers											
			0	1 14	1 28	1 56	1 112	1 224	1 448	1 896	1 1792	1 3584	1 7168	1 14000
Normal controls	100	100	34	17	27	11	8	3						
Primary atypical pneumonia	91	254	11	8	8	8	10	6	5	13	7	13	1	1
Bacterial pneumonias (total)	24	91	5	5	5	3	2	4						
Pneumococcus pneumonia	8	25	3		2	2		1						
Pulmonary tuberculosis	4	8	2		1			1						
Minor infections of respira- tory tract	46	50	26	6	4	4	3	3						
Measles	24	36	3	4	5	4	4	2	1	1				
Rubella	9	9	3	1	3	1	1							
Mumps	37	40	17	10	1	6								
Mumps orchitis	18	20		3	5	4	3	1		1		1		
Mumps encephalitis	2	2				1	1							
Chickenpox	6	6		2		2	2							
Acute catarrhal jaundice	14	16	6	3	3	1	1							
Infectious mononucleosis	7	15				1		1		3	1	1		
Scarlet fever	26	39	6	2	3	4	5	3	1	1	1			
Rheumatic fever	22	30	7	7	4		1	2		1				
Gonorrhea	23	23	5	4	7	4	2	1						
Seropositive syphilis	8	8	4	1	1	2								
Filariasis	8	8	4	2	1	1								
Amebiasis	2	2	1	1										
Coccidiomycosis	1	1		1										
Total	472	758	134	77	81	57	43	27	7	20	9	15	1	1

throats of the many normal persons.<sup>7a</sup> However, in some of these cases, these organisms may have acted as secondary invaders as reported by Longcope<sup>7b</sup> and Thomas.<sup>8</sup>

For the patients with pneumonia the titration of hemagglutinins was usually done shortly after their admission to the hospital and at weekly intervals thereafter. For a few of them, we were able to follow the titer for as long as two to three months.

7 (a) Kneeland, Y, and Smetana, H. Current Bronchopneumonia of Unusual Character and Unknown Etiology, *Bull Johns Hopkins Hosp* 67 229, 1940. (b) Longcope, W. T. Bronchopneumonia of Unknown Etiology (Variety X). A Report of Thirty-Two Cases with Two Deaths, *ibid* 67 268, 1940. (c) Dingle, J. H., Abernathy, T. J., Barger, G. F., Budingh, G. H., Feller, A. E., Langmuir, A. R., Rueggsegger, J. M., and Wood, W. B. Primary Atypical Pneumonia, Etiology Unknown, *War Med* 3 223 (March) 1943. (d) Drew, W. R. M., Samuel, E., and Ball, M. Primary Atypical Pneumonia, *Lancet* 1 761, 1943. (e) Dingle and Finland.<sup>3</sup>

8 Thomas, H. The Role of Alpha Hemolytic *Streptococcus* in Pneumonia, *Bull Johns Hopkins Hosp* 72 218, 1943.

The cases of infectious mononucleosis were typical, as indicated by generalized lymphadenopathy, splenomegaly, lymphocytosis and the presence of "lymphoid" cells in the blood and the frequent finding of large amounts of sheep cell agglutinins in the serum. Fourteen jaundiced patients were considered to have acute catarrhal jaundice.

## RESULTS

The results of titrations of the serum for cold hemagglutinin in 472 subjects are presented in table 2 and chart 1. To make the various clinical groups studied more nearly comparable, only the initial titers obtained for patients with primary atypical pneumonia are compared with the highest values for the patients with other infections whenever more than one determination was made.

With this method, a cold hemagglutinin was detected in 338 serums (71.6 per cent). It is likely that the number would have been greater, if titers below 1:14 were determined. The high-

est values (above 1 224) were obtained with greatest frequency in patients with primary atypical pneumonia and infectious mononucleosis. Similar values were also occasionally obtained for patients with measles, mumps orchitis, scarlet fever and rheumatic fever but not for normal controls and for patients with the other infectious diseases studied.

**Normal Controls**—A cold hemagglutinin was found in 66 per cent of 100 serums obtained from normal hospital personnel. The titer varied from 0 to 1 56 in 89 per cent, and in half of the serums it was 1 14 or less. In 11 per cent it ran out to 1 112 or 1 224 (table 2).

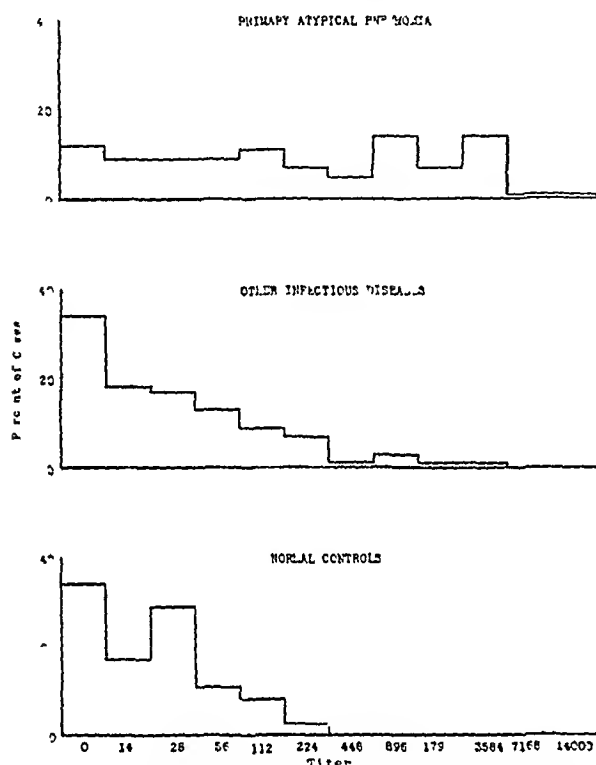


Chart 1—Percentage distribution of cold hemagglutinin titers of patients with primary atypical pneumonia, of patients with other infectious diseases and of normal controls.

Since an increased titer of cold hemagglutinin may be present for months after the recovery from primary atypical pneumonia and perhaps other infectious diseases as well, an attempt was made to determine whether the higher values in this group (1 112 and 1 224) were related to the recovery from a recent illness. Accordingly, the controls were divided into two groups on the basis of their histories, and the titers in each group were compared (table 3). Since all the controls were white persons, racial influences did not have to be taken into account. The relation of the various blood groups to the titer was not determined.

Of 38 controls who stated that they had had no colds, cough, sore throats or any known ill-

nesses for about six months, the cold hemagglutinin titer varied from 0 to 1 56 in 36 (93 per cent) and reached 1 112 in 2 persons. A comparison of the range of titer in men and in women revealed that titers of 1 56 or 1 112 occurred in 3 of 10 women and of 1 56 in 2 of 28 men. Although the numbers of subjects are small, it is possible that the distribution of the highest values in this subgroup of the normal controls was determined by sexual differences.

In 62 controls with histories of a recent acute infection of the respiratory tract or other infectious disease within a period of about six months, the titer exceeded 1 56 in 9 and ran out to 1 224 in 3. Although this group consisted of 9 women and 53 men, the highest titers occurred only in the men. They were found in 3 of 25 subjects with a history of a recent cough, in 2 of 8 with a history of sore throat, in 2 of 14 who had had a recent cold and in 2 subjects who had recently recovered from measles. A calculation of the statistical significance of the difference in the

TABLE 3—Relation of Cold Hemagglutinin Titer to a History of Recent Illness in Normal Controls

Group of Normal Controls	Num ber	Cold Hemagglutinin Titers					
		0	1 14	1 28	1 56	1 112	1 224
No history of recent illness	38	21	4	8	3	2	0
History of recent illness	62	13	13	19	8	6	3

incidence of titers above 1 56 between the two groups (by the method of chi square and with use of a probability of 0.05 as the limit of significance) indicated that a titer of 1 56 was probably related to a history of a recent infectious disease.

**Primary Atypical Pneumonia**—Of the 91 persons with primary atypical pneumonia, a cold hemagglutinin was detected in the serum on the initial examination in 80 (85.7 per cent). In 40 (44.9 per cent) the titer was greater than the highest value (1 224) seen in normal controls, and in 56 (61 per cent) it exceeded 1 56, the highest titer in 89 per cent of the controls. In 35 patients (38 per cent) the initial titer ran out to 1 896 or beyond. Values of 1 3,584 or more were obtained in 15 (16 per cent). The highest titers of cold agglutinin (1 7,168 and 1 14,000) encountered in the entire group of 472 subjects were obtained in the serums of persons with primary atypical pneumonia. On repetition of the titrations in the course of the syndrome, values above 1 56 occurred in 73 patients (80.2 per cent) and above 1 224 in 54 (59 per cent) (table 4).

On the other hand, in 18 patients (19.7 per cent) the highest cold agglutinin values did not exceed the dilution of 1:56, and in 19 others (20 per cent) the titer ranged from 1:112 to 1:224. In some cases these lower values could be attributed to a too short period of observation (see "Relation of Cold Hemagglutinin Titer to Other Features of Primary Atypical Pneumonia"), in others it may have been due to mis-

TABLE 4—Initial and Highest Cold Hemagglutinin Titers of 91 Patients with Primary Atypical Pneumonia

Titer	Initial	Highest
0	11	5
14	8	4
28	8	5
56	8	4
112	10	13
224	6	6
448	5	8
896	13	12
1792	7	12
3584	13	15
7168	1	4
14000	1	3
Total	91	91

takes in diagnosis. However, in 16 persons with primary atypical pneumonia, despite a sufficiently long period of observation during which repeated tests were run, a rise in cold agglutinin titer failed either to occur or to reach the levels obtained for most of the patients (table 8).

While the range of titer in this group of 37 patients with the lowest titers was similar to that for normal controls (0 to 1:224), the incidence of titers above 1:56 on the initial examination was much greater (43 per cent as compared with 11 per cent for normal controls).

**Bacterial Pneumonia**—In the 24 patients with bacterial pneumonia, a cold hemagglutinin when found was present in low titer, despite repeated tests during prolonged periods of observation (in persons with pneumococcic pneumonia for periods of eight to thirty-two days after the probable onset and in persons with the other bacterial pneumonias for periods of eight to ninety-three days). In the 8 patients with pneumococcic pneumonia the highest values were usually below 1:112. In 1 person, in whom the titer rose to 1:224 during convalescence, the sputum contained a type 12 pneumococcus and the roentgenologic findings and the course resembled those of many persons with primary atypical pneumonia. In 5 of the other 16 patients, the titer reached 1:112, or 1:224. In 4 of these 5 patients an empyema or pleural effusion developed, and in 3 the highest titer (1:112 or 1:224) was not apparent for fourteen to thirty-two days after the probable onset.

In summary, a comparison of the cold hemagglutinin titers in 91 patients with primary atypical pneumonia and in 24 with bacterial pneumonia shows that large amounts of cold hemagglutinin were present in the serum only in those with the former syndrome. In persons with uncomplicated pneumococcic pneumonia the cold agglutinin titers were usually low (0 to 1:56). In persons with bacterial pneumonia complicated by empyema and pleural effusion, the cold hemagglutinin values were observed to rise to 1:112 and 1:224 during the course of the disease in most instances. On the other hand, maximum titers of 1:224 or less were obtained also in 40 per cent of the persons with primary atypical pneumonia. Although for these patients this serologic test was not distinctive, titers of 1:112 and 1:224 were more common in patients with primary atypical pneumonia than in patients with bacterial pneumonia and in normal controls.

**Other Infections**—Of 257 patients with miscellaneous common infections exclusive of pneumonia, a cold hemagglutinin was detected in the serums of 173 (67.3 per cent). The titers exceeded 1:56 in 50 (19.4 per cent) and ran out beyond 1:224 in 13 (5.0 per cent). High titers comparable to those observed in the serums of persons with primary atypical pneumonia were frequently encountered in persons with infectious mononucleosis (table 5) and occasionally in patients with mumps orchitis, measles, scarlet fever and acute rheumatic fever.

TABLE 5—Laboratory Data for Patients with Infectious Mononucleosis

Case No.	Titer		White Blood Cell Count						
	Cold Agglu- tinin	Hetro- phile Anti- body	Total	Poly	Lym	Eosin	Mono	Baso	Lymph oid
1	1:3,584	1:1,792	8,500	12	84	2	2	0	+
2	1:224	1:448	14,500	14	80	2	4	0	—
3	1:56	1:1,792	20,000	21	76	0	3	0	+
4	1:1,792	1:14,000	7,500	12	88	0	0	0	±
5	1:896	1:3,584	8,600	23	77	0	0	0	—
6	1:896	1:112	5,350	46	51	1	2	0	+
7	1:896	1:28	5,600	42	50	6	2	0	+

In the subgroup of patients with the 5 infectious diseases mentioned (97 patients) in which the highest titers were observed the cold hemagglutinin titer exceeded 1:56 in 38 and 1:224 in 9. In this group, the incidence of titers above 1:56 was greater than in the group with other infections, in which the titer never exceeded 1:224. The statistical significance of this difference, however, was open to question on the basis of our data, since the tests were often repeated on the patients in the former group and not on those in the latter. On the other hand, it

is not unlikely that the incidence of serums containing cold hemagglutinin in patients with these 5 diseases and the height of the titers would approach the values for patients with primary atypical pneumonia if the numbers of patients with each disease studied and of titrations were similar

In the patients with infectious diseases (160) in whom the titer did not exceed 1:224, including those with minor infections of the respiratory tract, the titer exceeded 1:56 in 15. This figure was not significantly different from that for the incidence of such titers in normal controls. Of 46 patients with minor infections of the respiratory tract, titers above 1:56 occurred for 6. This figure was similar to that obtained for the 62 normal controls (14 per cent), many of whom gave a history of a recent infection of this type.

To summarize, the appearance of large amounts of cold hemagglutinin in the serum is not specific for primary atypical pneumonia among infectious diseases but may occur in certain other infections. These high titers, however, were limited to persons with 5 of 13 infections studied. In these the incidence of titers above 1:56 was higher than for normal controls and in the infections in which the titer did not exceed 1:224.

#### RELATION OF THE COLD AGGLUTININ TITER TO OTHER FEATURES OF PRIMARY ATYPICAL PNEUMONIA

Although it is clearly evident that a high level of serum cold agglutinin is observed in many patients with primary atypical pneumonia, little is known of the significance of this fact and its relation to other features of the syndrome. To obtain some data on these points, we compared the clinical observations with the cold hemagglutinin responses of 44 patients with primary atypical pneumonia. These patients were divided on the basis of cold hemagglutinin titer into three groups: (1) 15 patients with very high titers (1:1,792 or above) on admission to the hospital, (2) 13 patients with a rise in titer to a high level after admission, and (3) 16 patients in whom the cold agglutinin titer failed to exceed the highest values for normal controls and for patients with bacterial pneumonia and a variety of infectious diseases (table 2). Following is an analysis of some of the clinical features of each of these groups.

*Group 1*—The essential clinical findings for 15 patients with primary atypical pneumonia in whom very high levels of serum cold agglutinin were present on admission are shown in table 6. In most of these cases, the disease was extremely

mild and many of the patients seemed to be convalescing from a primary atypical pneumonia unrecognized for several weeks prior to entry. The period between the probable onset of the disease and admission to the hospital varied from five to thirty days (mode, ten to twelve days, average, thirteen days). In each instance, the patient sought admission because of persistent cough or the sudden onset of pain in the chest and fever after a variable period of cough. On admission, 10 patients had little or no fever, 5 patients were afebrile during the entire period of hospitalization, and in the others, the days of fever were usually less than seven. The white blood cell counts on admission varied from 7,300 to 24,600 but were usually between 7,000 and 11,000. The only other frequent hematologic observation was the presence of 4 to 10 monocytes in the differential white cell count (9 of 13 white blood cell counts). Roentgenograms of the chest showed only increased peribronchial and perivascular markings in 3 patients and slight evidences of pneumonic involvement in 9. In 2 of these, the roentgenologic abnormalities cleared in about ten days or less. Ten of these patients were treated symptomatically. Five were given sulfonamide compounds. Although in 1 patient so treated the temperature dropped to normal in twenty-four hours (case 12), in the other 4 the response to sulfadiazine was not dramatic. Eight of these patients left the hospital ten to twenty-one days after entry, with no or minimal residual symptoms or signs. The others were hospitalized longer because of persistent cough or thoracic findings. Pleural effusion was not noted in this group.

The case of 1 of these patients is worthy of special mention because it was very unusual in several respects and illustrates that the cold hemagglutinin response may precede definite roentgenographic evidence of primary atypical pneumonia by several weeks.

*CASE 8*—A 20 year old Negro seaman was admitted to the hospital with a history of persistent cough, substernal pain, sore gums and occasional chilly sensations for about two weeks. Two or three days prior to entry, he began to suffer from an intense headache associated with nausea and vomiting.

On admission, he appeared drowsy. His temperature was 99.4 F (oral), pulse rate 72 and respiratory rate 20. His cervical lymph nodes were palpable bilaterally, but there was no other adenopathy and the spleen could not be felt. The lungs were clear except for a few sticky rales on deep inspiration and after cough at the base of the right lung posteriorly. There was definite nuchal rigidity, and Kernig's sign was positive bilaterally. The only other positive finding was pronounced hypertrophic gingivitis.

Laboratory studies revealed a red blood cell count of 4,750,000, a hemoglobin content of 14.5 Gm, a white

TABLE 6—Essential Clinical Observations on Fifteen Patients with Primary Atypical Pneumonia with Very High Cold Hemagglutinin Titers on Admission to the Hospital

Case No	History	Admission Temperature, F	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Days		Complications and Residuals	Sulfa Admins diazine	Cold Agglutinin titer on admission
					Total	Poly	Lymph %	Eosin	Mono	Fever	Hospital			
1	Persistent cough, pain in chest, low grade fever and chilly sensation for 7 days	99	Diminished breath sounds, occasional rales in right lower part of chest posteriorly	Bilateral increase in perivascular and peribronchial markings	8,400	54	36	0	0	2	26	None	0	1 14,000
2	Coryza followed by dry cough for 10 days, sudden onset of pain in chest	98	Dulness, diminished breath sounds at base of left lung posteriorly	Diffuse mottling extreme left base, slight clearing in 11 days	7,300	63	33	0	4	0	10	Cough	0	1 7,168
3	Persistent cough, low grade fever for 10 days, sudden onset of pain in chest	99	Diminished breath sounds, coarse rales at base of left lung		None					0	30	Cough, roentgen shadow	0	1 3,584
4	Sudden onset of pain in chest and cough 20 days after onset of previous pneumonia	99	Moist rales at base of left lung	Small area of increased density at base of left lung	None					0	20	None	0	1 3,584
5	Coryza followed by cough for 14 days, pain in chest for 3 days	99	Dulness, diminished breath sounds, rales at base of left lung	Small area of increased density at base of left lung lateral to heart border	13,000	84	14	0	1	3	27	None	0	1 3,584
6	Fatigue, generalized aches, malaise, low grade fever 12 days	98.6	Bronchovesicular breath sounds, coarse rales at bases of both lungs	Heavy mottled density lower portion upper lobe right lung and in middle lobe of right lung, increased lung markings on left	7,450	68	26	0	6	2	26	Roentgenogram positive	0	1 3,584
7	Coryza followed by cough for 10 days, sudden onset of pain, in chest, chill, fever	102	Dulness, diminished bronchial breath sounds over entire lower lobe of left lung	Marked increase in density in middle third of left lung mottled density in upper lobe of right lung	7,500	64	28	2	6	5	27	None	+	1 3,584
8	Slight cough, sore chest, sore gums, fever for 14 days, headache for 3 days	99.4	Diminished breath sounds, rales at base of right lung	Increase in perivascular and peribronchial markings	16,500	74	22	0	4	4	18	None	+	1 3,584
9	Productive cough, malaise for 3 weeks	99	Chest normal	Blunting of left costophrenic angle, increase in peribronchial markings	8,600	48	45	0	7	0	35	None	0	1 3,584
10	Persistent cough, malaise, occasional fever 1 month, sudden onset of pain in chest, chills, fever	98	Diminished breath sounds, rales at base of left lung	Small area (6 cm in diameter) of increased density at base of left lung	10,950	79	12	4	6	0	21	Cough	0	1 3,584
11	Persistent cough, malaise, sweats, occasional low grade fever for 1 week	100	Diminished breath sounds at base of left lung	Diffuse area of increased density in middle third of left lung, clearing in 10 days	10,700	74	16	0	10	7	21	Cough, pain in chest	0	1 3,584
12	Coryza, cough, low grade fever for 1 week, sudden onset of pain in chest	102	Dulness diminished breath sounds at base of right lung posteriorly with coarse rales	Irregular area of infiltration in lower lobe of right lung	11,300	89	11	0	0	1	38	Cough	+	1 1,792
13	Headache, cough, chills, arthralgias for 5 days	102	Bronchovesicular breath sounds and rales at bases of both lungs	Mottled area of increased density in middle lobe, cleared in 10 days	13,500	59	32	2	7	5	21	None	0	1 1,792
14	Persistent cough for 16 days, sudden onset of fever	101.6	Bronchial breath sounds, rales at base of left lung	Mottled area of increased density in lower lobe of right lung	24,600	80	18	0	2	6	16	None	+	1 1,792
15	Fever for 2 weeks, cough, pain in chest for 1 week	104	Dulness, rales at base of right lung	Area of increased density at base of right lung medially	10,700	74	16	0	10	3	30	Malnutrition	+	1 1,792

blood cell count of 16,500, with 74 per cent polymorphonuclear leukocytes, 22 per cent lymphocytes and 4 per cent monocytes, examination of the urine for albumin, sugar and formed elements gave negative results, and the erythrocyte sedimentation rate (Cutler) was 24 mm in one hour. The Kahn reaction of the blood was negative.

A lumbar puncture yielded clear fluid under a pressure of 220 mm, which contained 68 mononuclear cells per cubic millimeter. The Pandy reaction was negative. The spinal fluid contained 48 mg of protein per hundred cubic centimeters. Culture of the spinal fluid was negative for bacteria.

A roentgenogram of the chest showed an increase in perivascular and peribronchial markings.

*Course*—The patient was given sulfathiazole in doses of 1 Gm every four hours for one week. His temperature became normal in four days, and he became more alert and responsive. A slight cough persisted.

*Special Studies*—Examination of the serum revealed a cold hemagglutinin titer of 1:3,584 within twenty-four hours after his admission to the hospital. This rose to 1:7,168 and was still 1:3,584 seventeen days after admission, when the patient returned to duty. A complement fixation test for lymphogranuloma venereum was negative. The patient's serum did not neutralize the viruses of St. Louis and Western equine encephalitis. The heterophile antibody titer was 0. The Weil-Felix reaction with *Proteus* OX-19 was negative.

*Second Admission*—The patient remained free of complaints for a period of five weeks. At the end of this time, he again began to cough, and after one week he suddenly experienced chilly sensations and a sharp pain in his right shoulder on inspiration.

Physical examination now revealed a temperature of 104 F, pulse rate of 92 and respiratory rate of 20. The patient was not dyspneic and did not appear acutely ill. On auscultation of the chest there was a leathery friction rub over the upper lobe of the right lung anteriorly and posteriorly, and the breath sounds were diminished in this area. The percussion note was dull. There were no other positive findings on physical examination.

The white blood cell count was 32,500, with 92 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes and 2 per cent monocytes. Sputum was difficult to obtain and did not reveal pneumococci, tubercle bacilli or other pathogenic bacteria. A spinal puncture revealed a normal spinal fluid pressure and yielded a clear fluid which still contained 14 cells per cubic millimeter. A roentgenogram of the chest now revealed a large homogeneous density involving the upper lobe of the right lung. The patient was given sulfadiazine in doses of 15 Gm every four hours. His temperature fell to normal in five days, but he continued to cough and to complain of pain in the shoulder for an additional five days. The roentgen shadow in the upper lobe of the right lung cleared almost completely in ten days.

The cold hemagglutinin titer on this admission was 1:448 and remained at this level for two weeks, after which the patient returned to duty.

*Summary*—In this case an acute meningeal reaction occurred in a patient whose serum revealed a high cold hemagglutinin titer (1:7,168). Although there was some evidence of a pulmonary involvement at this time, on physical examination, an atypical pneumonia was not apparent roentgenographically until about eight weeks later when there was a recurrence of cough and fever associated with pain in the shoulder and a homogeneous density in the right upper lobe.

*Group 2*—A rise in cold hemagglutinin titer from low or moderately increased levels to higher

ones was observed in 13 patients (table 7). The clinical findings and course varied widely in individual patients, but in general the entire group was characterized by a more acute onset of the syndrome (one to fourteen days) and a febrile course requiring longer periods of hospitalization than in group 1.

A significant increase in cold hemagglutinin titer was often apparent toward the end of the first week after the probable onset of the syndrome. Maximum titers were usually attained during the second and third weeks. However, this was not true of every patient. In 4, a significant increase in titer (above 1:224) was not observed for five or more weeks after the onset, and in 1 patient it did not occur until about eight weeks (chart 2). In 1 of these cases, a sharp increase in the titer of cold hemagglutinin was associated with a secondary rise in temperature and the occurrence of acute polyarthritides, pro-

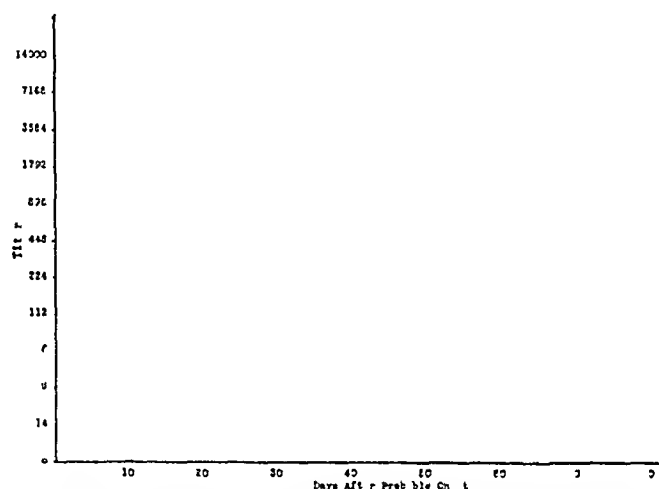


Chart 2—Relation between time after probable onset and cold hemagglutinin titer of 13 patients with primary atypical pneumonia (table 7).

ducing a syndrome resembling acute rheumatic fever, which has been noted previously in cases of primary atypical pneumonia.<sup>7a</sup> The pronounced rise in the cold hemagglutinin level was maintained only for a short time and fell to lower but still elevated values (1:448) as the fever and polyarthritides subsided. Prior to the recognition in recent years of the syndrome of primary atypical pneumonia, this case might have been considered as an example of rheumatic pneumonia.

A comparison of the findings and course of the 7 patients in whom the titer rose to high levels within three weeks and of the 6 in whom the rise in titer required a longer period indicated that the former had a shorter febrile course, with fewer complications and residuals.

Although based on observations on only a few patients, it is our general impression that a very

TABLE 7—Essential Clinical Observations on Patients with Primary Atypical Pneumonia Showing Rising Cold Hemagglutinin Titers

Case No	History	Admission Temperature, F	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Days		Complcations and Residuals	Cold Agglutinin Titer on Admission	Days After Onset	Highest Cold Agglutinin Titer	Days After Onset
					Total	Poly	Lymph	Eosin	Mono	Fever	Hospital					
1	Dry cough, low grade fever for 1 week	101.6	Moist musical rales, over entire left lung	Area of ill defined density at base of right lung, cleared in 9 days	18,800	88	8	2	2	1	27	None	1:448	12	1:1,792	18
2	Low grade fever for 4 days, cough for 1 day	101	Lungs clear	Small area of increased density at base of left lung just above diaphragm	11,100	72	24	0	4	4	12	None	1:14	4	1:448	9
3	Dry cough, fever, pain in chest for 2 days	100.6	Diminished breath sounds, fine rales at base of right lung, to and fro rub	Small infiltration in lower lobe of left lung	10,450	86	14	0	0	3	14	None	1:896	5	1:1,792	12
4	Dry cough, low grade fever for 1 week	101	Coarse wheezes, rales over both pulmonary fields	Early infiltration just above diaphragm on left	11,700	70	30	0	0	1	57	Mumps 1 month after admission	1:896	7	1:3,584	20
5	Dry cough for 1 week after recovery from measles	98.6	Coarse rales at bases of both lungs	Ill defined infiltrations in base of left lung extending to left hilus	12,200	64	26	0	0	14	26	Acute sinusitis, persistent cough	1:896	8	1:14,000	19
6	Sudden onset of dry cough, fever, chill, pain in right side of chest	102	Coarse rales, to and fro rub at base of right lung	Homogeneous density of upper lobe of right lung, cleared in 17 days	17,450	83	16	1	0	5	22	None	1:14	3	1:1,792	22
7	Slight cough, low grade fever, headache for 4 days	102	Chest clear	Fine mottling at base of left lung, cleared in 2 days	8,800	69	29	0	2	6	18	Slight	1:224	10	1:14,000	22
8	Cough, fever, chill, sore throat for 4 days	104	Dulness, bronchial breath sounds, friction rub at base of right lung	Area of increased density at base of right lung laterally	26,600	62	36	0	2	7	16	Pleurisy	1:14	7	1:448	24
9	Cough, fever, malaise, arthralgias for 2 days	101	Small area of bronchial breathing at base of right lung	Area of increased density at base of right lung medially	9,400	54	52	0	4	11	60	Acute arthritis, persistent cough	1:112	8	1:448	27
10	Sudden onset of fever, chill, pain in chest after cough and measles 2 weeks before	104	Bronchial breath sounds, dulness, to and fro friction rub at base of right lung	Area of increased density at base of right lung, extending from diaphragm to second rib	42,500	96	2	0	2	19	36	Pleural effusion	1:112	18	1:3,584	35
11	Malaise, low grade fever for 1 week, sudden onset cough, pain in right side of chest	105	Dulness, diminished breath sounds, rhonch at base of right lung	Area of increased density in upper part of lower lobe of right lung	17,300	91	6	0	3	30	53	Pleural effusion, persistent cough, arthritis	1:112	9	1:3,584	40
12	Dry hacking cough for 4 weeks following acute catarrhal fever, sudden onset of pain in chest, high fever, sputum	100.6	Dulness, diminished breath sounds below angle of left scapula	Small area of increased density extreme left base, cleared in 1 week	6,800	56	36	2	2	1	19	Cough	1:448	36	1:1,792	42
13	Headache, low grade fever, pain in chest for 3 days	102	Dulness, diminished breath sounds at base of left lung	Small area of increased density at base of left lung	17,000	80	18	0	2	63	73	Pleurisy, persistent cough	1:28	5	1:1,792	73

high cold hemagglutinin titer on admission to the hospital or a rapidly rising titer (within two or three weeks) seemed to herald a favorable prognosis. On the other hand, a slowly rising titer of cold hemagglutinin was usually indicative of a prolonged illness.

*Group 3*—In 16 patients, followed for periods of twenty-two to sixty-one days after the probable onset of the syndrome, the cold hemagglutinin titer did not rise above the highest values seen in normal controls and in patients with a variety of acute infections (1:112 or 1:224). Although cold hemagglutinin was demonstrated in each of these patients, in 7 the titer failed to exceed 1:56 and in 9 it rose slowly to 1:112 and 1:224 or remained fixed at these levels (table 8).

In this group, the clinical findings were similar to those of the sicker patients in group 2 (with a slowly rising titer). Three patients gave a history of a previous attack of pleuritic pain and fever within the past year. One patient was seen with a recurrence of fever, pain in the chest and cough immediately after a thirty day period of hospitalization for primary atypical pneumonia.

Ten patients were admitted within seven days after the onset of symptoms, 6 patients had symptoms for a longer period prior to entry. All were febrile on admission, and in ten the admission temperature was 102 F or above. The white blood cell counts varied from 4,150 to 14,100 and were below 9,000 in 10 patients. Only 1 patient had more than 4 monocytes in the differential count. The roentgenologic observations did not differ from those of some of the patients in the other groups with primary atypical pneumonia, and the response to sulfadiazine was disappointing.

The febrile course was usually prolonged and exceeded one week in 9 cases. Seven patients had low grade fevers (temperatures up to 101-102 F) for two to six weeks. The periods of hospitalization were correspondingly long and were more than twenty-one days for 11 patients. Eight of these patients still complained of cough when they left this hospital. Four had pleural effusions requiring further convalescent care.

Although the syndrome seemed somewhat more prolonged in this group and the incidence of complications and residual symptoms was higher, the only striking difference was the failure of the cold hemagglutinin level to reach the increased values observed in 60 per cent of the patients with primary atypical pneumonia. The reasons for this were not apparent, but the following possible explanations were considered: 1. Certain etiologic agents causing the syndrome of atypical pneumonia may fail to call forth a cold hemagglutinin response. 2. In certain patients with

primary atypical pneumonia, the response may not occur for long periods (as in case 10, group 2). 3. In some instances it may have been impossible to distinguish between primary atypical and bacterial pneumonia.

#### COMMENT

This study confirms previous observations that human serum frequently contains a cold hemagglutinin for homologous erythrocytes (group O).<sup>9</sup> As suggested by Kettel,<sup>10</sup> this may be a universal property of human serum. With a method involving a long period of refrigeration of the cell suspensions and a microscopic reading of the end point, cold hemagglutination was commonly noted in normal serum dilutions through 1:56. Slightly higher values (1:112 and 1:224) were observed occasionally in the serums of normal persons (11 per cent). It seemed logical to regard these higher values as possible reactions to recent acute infectious diseases, since it is known that the serum cold hemagglutinin level increases during convalescence from certain infections, for example, primary atypical pneumonia.

If it is assumed that a titer of 1:56 is the upper limit of cold agglutinin activity in most normal serums with this serologic method, then slight increases in titer were noted in the serums of patients with almost every infection studied. This suggests a nonspecific stimulation of the tissues involved in the production of cold hemagglutinin by a wide variety of infectious agents. On the other hand, since great increases in cold hemagglutinin titer were observed in the serums of patients with a smaller group of diseases, it seemed that certain infectious agents are capable of eliciting a more intense reaction of this type than others. However, these intense responses as well as the mild ones were relatively nonspecific.

Although the mechanism of the production of cold hemagglutinin in large amounts in persons with certain infectious diseases is unknown, many of the conditions in which this was noted are characterized by the appearance of large amounts of specific antibodies in the serum. In these conditions cold hemagglutination may be a manifestation of the presence of distinct but chemically related antibodies. Another explanation, suggested by Belk,<sup>11</sup> who studied a cold agglutinin in a case of infectious mononucleosis,

9 Kettel, K. Recherches sur les agglutinines au froid dans les serums humains, *Compt rend, Soc de biol* 100 371, 1929.

10 Kettel, K., cited by Stats and Wassermann.<sup>5</sup>

11 Belk, W. Minor Hemagglutinins, *J Lab & Clin Med* 20 1035, 1935.

TABLE 8—Essential Clinical Observations on Sixteen Patients with Primary Atypical Pneumonia with Low Cold Hemagglutinin Titers

Case No	History	Admission Temperature, F	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Sulfa diazine	Complications and Residuals	Highest Days Cold After Agglu tinin Titer Onset
					Total	Poly	Lymph	Eosin	Mono			
1	Chronic cough with yellow blood streaked sputum for 2 weeks, chills, fever, pain in chest for 1 day	102	Dulness, diminished breath sound at base of left lung, rales at bases of both lungs	Small area of consolidation at base of right lung medially	8,700	61	37	0	2	5	30	41
2	Sudden onset of cough, fever, chills 2 days before admission	100	Dulness, diminished breath sounds at base of left lung and upper lobe of right lung	Area of increased density in upper third of right pulmonary field	5,600	38	40	0	2	2	0	44
3	Productive cough, pain in left side of chest for 2 weeks, acute pain in chest on inspiration for 2 days	101.8	Dulness, diminished breath sounds at base of left lung	Small area of increased density at base of left lung laterally, fluid present 1 week after admission	7,100	69	27	2	2	27	34	48
4	Dry cough, malaise, anorexia, low grade fever for 10 days, pain in chest for 8 days, pleurisy 1 year ago	100	Fine crepitant rales at base of right lung, rhonchi throughout both lungs	Area of increased density in middle third of left lung	8,700	72	26	2	0	5	26	35
5	Persistent productive cough for 2 weeks, bloody sputum 2 days before admission	103.6	Roughened breath sounds, bubbling rales at base of left lung	Small area of increased density overlying domes of diaphragm on each side, clear in eleven days	7,300	50	40	2	8	7	21	35
6	Pain in right side of chest and dyspnea after acute catarrhal fever for 1 week	99.5	Dulness, bronchial breath ing, fine rales at base of right lung	Obiteration of right costo phrenic angle and diffuse infiltration in this area	10,500	68	28	0	1	14	72	61
7	Cough, chilly sensations, low grade fever for 2 weeks, sudden onset of high fever	104.5	Scattered rhonchi bilater ally, fine rales at angle of left scapula	Area of increased density left midpulmonary field, blunt ing of right costophrenic angle	7,900	70	28	0	2	11	17	31
8	Productive cough for 1 week, chills, fever for 1 day	103	Sonorous rales at bases of both lungs	Small area of increased density at base of left lung, no evidence of bronchiectasis	11,150	64	34	0	2	36	36	40
9	Sudden onset of cough, fever, chest pain on inspiration, similar attack 2 months previously	103.2	Dulness, diminished breath sounds at base of right lung and in right scapular region	Area of increased density in upper lobe of right lung	12,600	80	18	0	2	14	26	23
10	Persistent cough for 1 week sticking pain in left side of chest for 1 day	101	Diminished breath sounds, fine rales at bases of both lungs	Area of increased density at base of right lung medially, no change in 1 week	8,600	67	31	0	2	16	30	27
11	Dry cough, pain in right side of chest for 1 week	99	Dulness, decreased breath sounds at base of right lung	Area of increased density at base of right lung, some obiteration of left costo phrenic angle	11,500	80	20	0	0	9	20	22
12	Severe productive cough, malaise, low grade fever for 2½ weeks, pain in chest for 1 day	100	Rales at bases of both lungs	Multiple areas of increased density at bases of both lungs	12,000	73	25	0	2	18	26	26
13	Recurrence of pain in left side of chest, chills, fever for 1 day, 1 week after attack of atypical pneumonia	99	Dulness, diminished breath sounds in lower lobe of left lung	Area of increased density in middle lobe and at base of left lung, some fluid 1 week later	6,800	11	50	2	4	6	30	49
14	Sudden onset of fever, chills nonproductive cough 20 hours previously	103	Few coarse rales at base of left lung	Exaggeration bronchial markings in both lungs, massive pleural effusion	10,500	86	12	0	2	10	46	30
15	Coryza, low grade fever for 6 days, followed by sudden onset of fever, chill, pain in right side of chest	104	Dulness, bronchovascular rhonchi at base of left lung	Increased density in mild portion of left pulmonary field	4,150	70	38	0	2	6	28	25
16	Chronic cough for 1 month, sudden onset of high fever, productive cough, pain in chest	103.4	Mild dyspnea, dulness, bronchial breath sounds at base of left lung	Increased density in lower third of left pulmonary field	13,100	88	8	0	4	7	21	54

is that cold hemagglutination is due to purposeless and excessive production of antibodies under certain conditions of nonspecific stimulation

A further point in favor of the nonspecific, or general, character of the phenomenon of cold hemagglutination in infectious diseases is the fact that the serums in which it occurs to a significant degree frequently react positively for syphilis. These reactions are common in trypanosomiasis, malaria and infectious mononucleosis and have been observed in other acute infections, including primary atypical pneumonia.<sup>12</sup> Moreover, a reagin of the type giving a positive Kahn or Wassermann reaction has been found in small amounts in normal human serums and at times in sufficient quantity to give a positive reaction for syphilis in a perfectly normal person.<sup>13</sup> It is interesting and perhaps has some bearing on the nature of cold hemagglutination that the general biologic type of Kahn precipitation reaction occurs strongly at 1 C while the true syphilitic reagin is maximally active at 37 C and inactive at 1 C.<sup>14</sup> The apparent relation of nonspecific serologic reactions to low temperatures is further indicated by the finding that cold seems to increase the activity of sheep cell agglutinins in infectious mononucleosis.<sup>14</sup>

The frequent presence of extremely high titers of cold hemagglutinin in persons with primary atypical pneumonia alone of the common diseases of the respiratory tract studied is a serologic observation of value in confirming the diagnosis of the syndrome in most cases and in differentiating it from pneumonia of other common causes. However, the characteristic sharp elevations in cold agglutinin concentration were not observed in an appreciable number of persons with primary atypical pneumonia. In our opinion, the test was of least value as a differential finding in cases in which the greatest difficulty was encountered in distinguishing primary atypical from bacterial pneumonia. It is possible, however, that some cases in which slight elevations in titer were noted in convalescence were instances of infections with more than one agent (1 e virus and bacteria)

A correlation of the cold agglutinin response and the clinical observations in cases of primary atypical pneumonia indicated that this reaction

may have prognostic value. The type of response seemed to be related to the course of the disease. It occurred promptly and was most intense in the cases of mild disease and slow in developing and often slight in the cases in which the course was prolonged and marked by complications. This behavior of the cold hemagglutinin response favors the concept that it is a manifestation of immunity.

The test in our hands has been of definite assistance in case finding and has led to the recognition of several cases of mild primary atypical pneumonia that may not have been noted if this test had not been done. Titration of the serum for cold hemagglutinin is advised for all patients with persistent cough and obscure pulmonary abnormalities on physical and roentgenographic examination. The failure to observe high titers of cold agglutinin in patients with a variety of minor infections of the respiratory tract and in a group of normal persons who had recently recovered from such infections suggests that it is of doubtful value in detecting the carrier state and minor infections with the agent or agents causing atypical pneumonia. However, since we had no data concerning the number of actual infections with or exposures to such agents, an evaluation of the test as a tool in studying the epidemiology of primary atypical pneumonia must await the definite recognition of the agents causing the syndrome.

#### SUMMARY

1 A cold hemagglutinin against human group O erythrocytes was detected in 72 per cent of 472 subjects, including 115 with pneumonia, 257 with other infections and 100 normal controls

2 In normal controls, the cold hemagglutinin titer was usually 1:56 or lower (89 per cent) and reached 1:112 and 1:224 in 11 per cent. Recovery from recent acute infection seemed significantly to affect the cold hemagglutinin level of the serum in normal controls

3 The highest values of cold hemagglutinin were found most frequently in patients with primary atypical pneumonia, but in 40 per cent of persons with this syndrome the titer did not exceed the highest titer (1:224) in normal controls and in persons with a variety of acute infections

4 In patients with bacterial pneumonia, the cold hemagglutinin values were usually lower than in patients with primary atypical pneumonia. Slight elevations in titer equaling the highest titer in 25 per cent of the patients with atypical pneumonia occurred in patients with bacterial

<sup>12</sup> Taussig, A. E. On the Persistence of Falsely Positive Serologic Tests for Syphilis in Non-Syphilitic Infections, *J. Lab. & Clin. Med.* **29**: 473, 1944

<sup>13</sup> Kahn, R. L. The Verification Test in the Serology of Syphilis, *J. Lab. & Clin. Med.* **28**: 1175, 1943

<sup>14</sup> Spingarn, C., Jones, J. P., and Owrutsky, B. A Note on the Occurrence of Cold Hemagglutination in Infectious Mononucleosis. *U. S. Nav. M. Bull.* **43**: 717 (Oct) 1944

pneumonias complicated by empyema or pleural effusion

5 High values of cold hemagglutinin were noted in patients with infectious mononucleosis, mumps orchitis, measles, scarlet fever and rheumatic fever

6 In patients with primary atypical pneumonia, a high titer on admission or a rapidly rising titer seemed to indicate a favorable prognosis

7 Patients with primary atypical pneumonia in whom high titers of cold hemagglutinin were

not observed usually had a prolonged illness in which pleural complications were frequent

8 It is possible that cold hemagglutination is a nonspecific manifestation of certain types of antibody response

Captain J H Robbins, MC, U S N, the Commanding Officer of the Naval Hospital, Treasure Island, and Captain E J Best, MC, U S N R, Chief of Services, gave advice in this study Dr G Meiklejohn performed the complement fixation and neutralization tests in case 8 Valuable technical assistance was given by Chief Pharmacist Mates B Owrutsky, J Coyner, L Dodge and Pharmacist Mates, First Class, S Spangler and H Spikes

# AMEBIC PERICARDITIS

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Pericarditis is a rare complication of amebiasis. A review of the literature revealed only 22 proved cases<sup>1</sup>. The literature contains a number of reports of pericardial involvement in the course of hepatic abscess of probable, but not proved, amebic nature. Some of these cases occurred before the discovery of *Endameba histolytica*.

In a recent review amebic hepatitis and hepatic abscess were extensively discussed by Ochsner and DeBakey<sup>1a</sup>. These authors stated that various surveys of the population of the United States have shown the incidence of amebiasis to be between 5 and 20 per cent. The incidence of associated hepatitis and hepatic abscess varies considerably in different statistical analyses. As was pointed out by Ochsner and DeBakey, this incidence is significantly higher in the cases in which autopsies were performed than in the clinically observed cases. These authors collected a series of 5,211 fatal cases of amebiasis and noted that in 36.6 per cent of these the liver was involved. The incidence in the various groups of this series varied between 7.6 and 84.4 per cent. In a series of 9,696 cases of clinical amebiasis assembled from the literature, hepatic abscess was present in 48.6 per cent.

The purpose of this report is to present a case of amebic pericarditis secondary to extension of an amebic abscess of the liver. In this case the correct diagnosis was made only at autopsy.

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1 (a) Ochsner, A., and DeBakey, M. Amebic Hepatitis and Hepatic Abscess, *Surgery* **13** 460 (March), 612 (April) 1943. (b) Vergoz and Hermenjat-Gerin. De la rupture des abces amibiens du foie dans les cavites sereuses (pleure, peritoine, pericarde), *Rev de chir*, Paris **51** 680 (Nov) 1932. (c) Huard, P., and Meyer-May, J. Les abces du foie, Paris, Masson & Cie, 1936. (d) Craig, C. F. The Complications of Amoebic and Specific Dysentery, as Observed at Autopsy. An Analysis of One Hundred and Twenty Cases, *Am J M Sc* **123** 145 (Aug) 1904. (e) Howard, W. T., and Hoover, C. F. Tropical Abscess of the Liver, *ibid* **114** 150 (Aug) 1897. (f) Surbek, K. E. Ein Fall von Amoben-Pericarditis, *Arch f Schiffs- u Tropen-Hyg* **34** 456 (Aug) 1930. (g) Kataropula, A. Amobenperikarditis, *ibid* **36** 544 (Oct) 1932.

## REPORT OF A CASE

*History*—A 17 year old Negro entered Grady Hospital in March 1944. Because of pain and tenderness in his left flank and costovertebral angle, he was admitted to the genitourinary service with a diagnosis of perinephric abscess.

The patient had been in apparently good health until three months prior to admission to the hospital, at that time he noted the gradual onset of pain in the right shoulder, which persisted intermittently until his admission. During the same period he complained of malaise and progressive loss of appetite and of weight. Approximately two months prior to admission he noticed pain in the lumbar region, at first in the midline. It rapidly spread to both flanks and was particularly severe on the left. During the three weeks preceding admission he had profuse nocturnal sweats and fever without chills. He occasionally noted a pain in both sides of the chest but had no cough. In the week before admission he frequently complained of periumbilical pain and of a sharp pain in the left flank, which radiated toward the left axilla.

There was no history of diarrhea, and the remainder of the review of the systems failed to reveal anything significant.

The past history and the family history were non-contributory.

*Physical Examination*—On his admission the patient's temperature was 100.8 F, his pulse rate 105 per minute, his respiratory rate 22 per minute and his blood pressure 90 systolic and 60 diastolic. He was acutely ill. The significant physical findings were limited to the chest and the abdomen.

The heart was slightly enlarged to the left, and there were a loud pleuropericardial friction rub and a thrill over the lower left side of the precordium. No murmurs were heard. There was normal sinus rhythm. A few moist rales were heard over the bases of both lungs, especially the right, otherwise the lungs showed no abnormalities on physical examination. There was tenderness in both flanks and costovertebral angles, more marked on the left. The liver was palpated 4 finger-breadths below the right costal margin, it was not tender.

*Laboratory Data*—On the patient's admission the only significant laboratory finding was a white blood cell count of 20,800, with 86 per cent neutrophils and 14 per cent lymphocytes. The count ranged from 13,000 to 39,000 on many subsequent examinations during his thirty-nine day stay in the hospital. The results of urinalysis were essentially normal at all times. There was mild secondary anemia. The erythrocyte sedimentation rate was 64 mm in one hour (Westergren). The Kahn reaction of the blood was negative. Examination of the stool failed to show the presence of blood (guaiac test). Repeated cultures of blood were sterile. A tuberculin test (purified protein derivative, first strength) elicited a positive reaction. A retrograde pyelogram and a roentgenogram of his chest

taken the day after his admission were interpreted as normal. A lumbar puncture yielded no significant information.

*Course*—During the first six days in the hospital the patient's temperature varied between 100 and 102 F, clinically there was no significant change except for development of a sharp precordial pain on the sixth day. On the next day this became severe, and there were signs of peripheral circulatory collapse, with a blood pressure of 70 systolic and 60 diastolic. The veins of his neck were distended, and his pulse was strikingly paradoxical. A roentgenogram of his chest at this time revealed that the heart was considerably larger than previously, with a shortened cardiac pedicle. On fluoroscopic examination no pulsations of the ventricles could be seen. Pleural thickening along both axillary lines and a small area of increased density in the right costophrenic angle were also reported.

A diagnosis of pericardial effusion was made, and the patient was transferred to the medical service, where an immediate pericardial paracentesis resulted in dramatic clinical improvement. Six hundred cubic centimeters of thin, chocolate-colored material was withdrawn. This fluid contained 45,000 red blood cells and 110,000 white blood cells, 88 per cent of which were polymorphonuclear leukocytes. Frequent pericardial taps were performed thereafter, several of them were necessitated by symptoms of tamponade. Each time 250 to 850 cc of fluid was removed, this became progressively thicker and changed from chocolate brown to brick red. The number of white blood cells in this exudate fell to 8,000 per cubic millimeter, with 44 per cent polymorphonuclear leukocytes. The fluid was cultured repeatedly on routine mediums, as well as on Petragnani's medium, and was sterile at all times. Numerous smears were examined for tubercle bacilli and other bacteria, but none were seen. Several wet preparations of this material were studied by competent observers, and no parasites were noted. On the patient's ninth day in the hospital the entire right pleural cavity was found to be filled with fluid. Despite a thoracentesis this reaccumulated rapidly. This fluid was clear and straw colored, and a culture of it was sterile. The patient had gross hemoptysis on the twenty-seventh day in the hospital, but this condition lasted for only a few days and the amount of sputum was small. His temperature fluctuated between 98 and 102 F. He was treated with sulfamerazine for one week, without improvement, thereafter, therapy was symptomatic.

Repeated roentgenographic examinations of his chest revealed that his heart had become globular and had remained large. Several electrocardiograms taken after the development of pericarditis showed only isoelectric T waves in leads I and II.

His liver decreased slightly in size, and a small amount of fluid appeared in the peritoneal cavity shortly before death. The pleuropericardial friction rub persisted. The course was downhill, and the patient died on the thirty-ninth day in the hospital. Despite failure to identify the tubercle bacillus by culture or smear, the clinical impression at the time of death was tuberculous pericarditis.

*Autopsy*—Autopsy was performed six hours after death. Permission for examination of the brain was not granted. Only the pertinent data are given here.

*Gross Examination*—The parietal pericardium was thickened and measured 4 to 5 mm in thickness. The pericardial cavity contained a few cubic centimeters of thick, greenish-yellow, odorless purulent material, which was adherent to both the visceral and the parietal surface. These were yellowish gray and granular. The

epicardium was also greatly thickened, and the usual landmarks were obscured. There were no pericardial adhesions. Extensive fibrinous pleuropericardial adhesions were seen on both sides. The right pleural cavity contained 3,700 cc of light chocolate brown fluid, and the pleural surfaces were covered by shaggy, friable, greenish yellow exudate. The right lung (370 Gm) was collapsed and displaced toward the mediastinum. The interlobar septums were obliterated by dense fibrinous adhesions. The lower lobe was consolidated, and its posterior lateral third consisted of friable, somewhat necrotic, greenish gray to greenish brown tissue, in which there were numerous rather poorly demarcated abscesses. These varied in diameter from 0.5 to 2 cm and were filled with viscous, greenish yellow material. In addition, there were several firm, elevated, brownish red nodules. The upper and middle lobes were atelectatic. The left lung (200 Gm) and the pleural cavity appeared normal.

The peritoneal cavity contained 200 cc of clear yellow fluid. The liver weighed 1,200 Gm. In the right lobe of the liver, immediately beneath the diaphragm, there was a large abscess. This measured 11 cm in width, 5 cm in anteroposterior diameter and 5 cm in depth. The diaphragm could not be definitely identified in this region. The pericardium appeared to form the superior wall of the abscess, and it extended laterally beneath the right diaphragmatic pleura. The abscess was filled with friable, yellowish green material, similar to that in the pericardial cavity. The inferior vena cava passed through the center of the abscess, and shaggy exudate was adherent to it. A firm, grayish white wall, 3 to 4 mm thick, separated the abscess cavity from the surrounding hepatic parenchyma, which was compressed, greatly congested and scarred. The remainder of the liver was congested, and its lobular pattern was not distinct. Numerous tiny nodules were palpated on its cut surfaces, but these could not be seen. No communication could be demonstrated between the hepatic abscess, on the one hand, and the pericardial or the pleural cavity, on the other. There was no broncho-pleural, bronchohepatic or bronchopericardial fistula.

Careful examination of the entire alimentary tract, from the esophagus to the anus, failed to reveal any evidence of ulceration, inflammation or scarring. There were no other significant findings on gross examination of the heart, spleen, pancreas, kidneys, adrenals, aorta, gallbladder, bladder, genitalia and other structures.

*Escherichia coli* was cultured from the pericardial cavity, the right pleural cavity, the right lung and the spleen.

*Histologic Examination*—Blocks of all tissues were fixed in Zenker's fluid with 5 per cent glacial acetic acid and in solution of formaldehyde U S P, diluted 1 to 10. The phloxine-methylene blue stain was used routinely, and phosphotungstic acid hematoxylin (Mallory's modification for amebas) was used when indicated.

Both the parietal and the visceral pericardium were considerably thickened. They consisted in general of rather dense fibrous connective tissue, but in some areas this was loosely arranged. The surfaces were covered by a thick layer of necrotic material backed by granulation tissue, with numerous large mononuclear cells and some lymphoid and plasma cell elements and a few polymorphonuclear leukocytes. Within the necrotic material the ghostlike outlines of the involved tissues could still be made out. The granulation tissue immediately adjacent to the necrotic material showed evidence of similar lytic necrosis (fig 1 A). Innumerable typical amebas were noted in the necrotic tissue and in the deeper layers of the pericardium but none in the other

layers of the heart. They were also common in the capillaries and small veins. The amebas were found singly and in clusters of three or four (fig 1 *B*). They were always surrounded by a small halo of cytolysis. They frequently contained phagocytosed red blood cells.

pericardium, which showed varying degrees of obliterative changes. There were no other significant findings in the heart.

The pleura was thickened and fibrosed. Its surface was covered by necrotic material, similar to that described in the pericardium. It also contained numer-



Fig 1—*A*, parietal pericardium covered on the cardiac surface with a thick layer of exudate. Note the characteristic lytic necrosis of the tissue and the comparatively slight degree of inflammatory cell infiltration. Phloxine-methylene blue,  $\times 60$ . *B*, several amebas within a capillary of the parietal pericardium. Phosphotungstic acid hematoxylin,  $\times 520$ . *C*, early amebic abscess in the right lung, involving a bronchus. Relatively uninvolved pulmonary tissue is seen in the upper part of the picture. Phloxine-methylene blue,  $\times 60$ .

The myocardium immediately beneath the epicardium was pale and edematous. The blood vessels were normal with the exception of some in the deeper layers of the

out typical amebas, and there was evidence of beginning organization. Throughout the pulmonary parenchyma there were numerous abscesses of varying size and age.

(fig 1 C) Many of the abscesses appeared to be confluent, and the bronchi were often involved. Early abscesses were characterized by lytic necrosis of the tissue, some hemorrhage and fibrosis, but there was little cellular response. The older abscesses showed ragged walls of fibrous tissue lined with necrotic material, as previously described. Numerous amebas were seen in the abscesses and their walls (fig 2 A). The involved bronchi showed chronic inflammation of their walls and contained many amebas in the lumens and walls. The intervening, uninvolved, parenchyma displayed edema, congestion and numerous large, pigment-laden mononuclear cells in the alveoli, as well as chronic bronchitis. There were no other significant findings in the lungs.

The abscess in the liver was located close to the capsule, which it involved. The abscess wall and its contents displayed the same characteristics as were described in the lung and the pericardium (fig 2B), and, again, amebas were numerous in the wall, as well as among the necrotic contents. The hepatic tissue surrounding the abscess showed marked distortion of its

**Anatomic Diagnosis** The diagnosis was amebic abscess of the liver, amebic pericarditis, amebic pleuritis on the right side, multiple amebic abscesses of the right lung, fibrosis of the liver (weight, 1,200 Gm), fibrosis of the spleen (60 Gm), bilateral fibrinous pleuropericardial adhesions, ascites (200 cc), pronounced congestion of the viscera, hyperplasia of the bone marrow, and emaciation.

#### COMMENT

The patient's clinical picture was dominated by the obvious pericarditis. Because of this, little attention was paid to the history of pain in the right shoulder three months prior to his admission and the abdominal pain shortly preceding his entry, two symptoms which should have directed attention toward a possible hepatic abscess. Similarly, the important roentgenologic finding of a bilaterally elevated diaphragm was

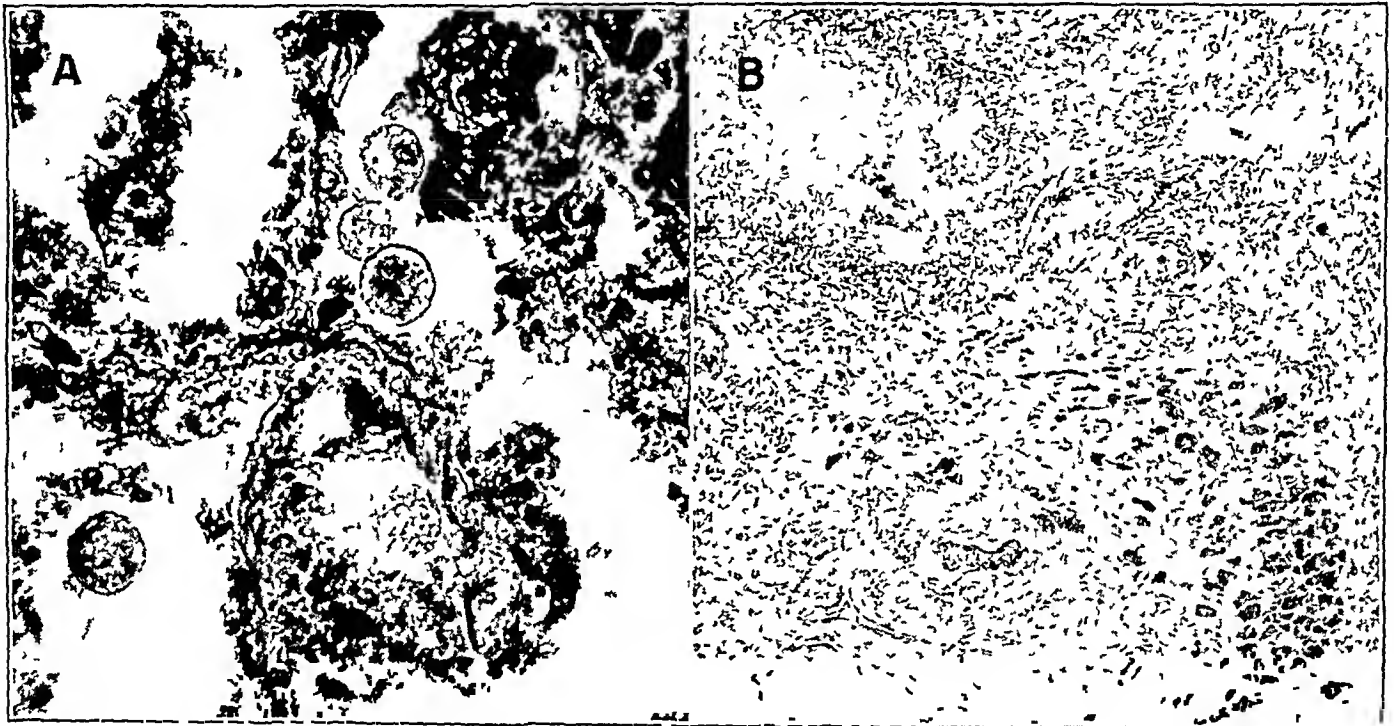


Fig 2—A, several amebas within the alveoli. The septums show early lytic necrosis. Phosphotungstic acid hematoxylin,  $\times 412$ . B, a corner of the amebic abscess of the liver surrounded by a thick layer of old granulation tissue. Some bile ducts and hepatic cells are seen in the lower right corner. Phloxine-methylene blue,  $\times 50$ .

architecture, with extensive old and recent hemorrhages. Elsewhere the architecture of the liver was greatly altered, this change was caused by extensive old scarring of irregular distribution. In some areas it appeared to involve the centrilobular and midzonal areas more than the portal spaces. No significant amount of proliferation of bile ducts had taken place, but in many regions the hepatic cells had a definitely regenerative appearance. No amebas were seen outside the abscess. There were pronounced congestion and edema throughout, with increased activity of the Kupffer cells.

Other histologic changes noted included slight diffuse fibrosis of the spleen, hyperplasia of the bone marrow and slight chronic cystitis. Sections of the stomach and the large intestine were normal. The wall of the gallbladder was slightly edematous, but there was no evidence of an inflammatory process. The tracheo-bronchial and mesenteric lymph nodes showed hyperplasia but no amebiasis.

not given proper consideration. All of these findings might have called attention to a hepatic or subdiaphragmatic abscess. In addition, the appearance of the material aspirated from the pericardial cavity should, at least in retrospect, have cast doubt on the diagnosis of tuberculous pericarditis. This material was thin and chocolate colored and corresponded to the characteristic description of the contents of an amebic abscess of the liver.

Although this fluid was examined by observers well acquainted with the appearance of amebas, none were found. However, the diagnosis of amebiasis was not entertained at this time. It is sometimes stated that amebas are not encountered in the contents of a hepatic abscess.

but appear only in its wall MacCallum<sup>2</sup> pointed out that this may be true at the time of the first aspiration but after the abscess has been exposed to air amebas rapidly appear in its contents In this case, as has already been described, histologic examination revealed numerous amebas in the necrotic material, as well as in the wall of the abscess Of 873 cases of amebic abscess of the liver collected from the literature by Ochsner and DeBakey,<sup>1a</sup> amebas were demonstrated in the contents of the abscess in 37.8 per cent However, in their own series of 91 cases in which such an examination was performed positive results were obtained in only 16.5 per cent

Rupture of an amebic abscess of the liver into the lung, the pleural cavity or both is not an uncommon complication Ochsner and DeBakey<sup>1a</sup> stated that this may occur in approximately 15 per cent of cases In the present case, an extension of the amebic infection from the liver into the pericardium, the right pleural cavity and the lung had occurred Furthermore, the pulmonary amebic abscesses showed extensive communication with the bronchi, many of which contained numerous amebas Thus there existed the possibility of a more generalized amebic pneumonia involving both lungs and of a secondary involvement of the alimentary tract by swallowing the organism However, there was no evidence of such a spread of the infection

It is of interest that no signs of active or healed intestinal amebiasis were encountered in this case It should be kept in mind that healed lesions in the intestine may be overlooked

<sup>2</sup> MacCallum, W. G. *A Textbook of Pathology*, Philadelphia, W. B. Saunders Company, 1932

The gross and histologic appearance of the liver in this case was somewhat unusual It was characterized by fibrosis which did not conform to any of the usual types of cirrhosis of the liver or to that of chronic passive congestion On the whole the picture suggested the end stage of marked diffuse hepatitis, and one might assume that this had been amebic in nature Ochsner and DeBakey,<sup>1a</sup> in discussing the histopathology of amebic hepatitis, mentioned a similar observation

Huard and Meyer-May<sup>1c</sup> reported recovery of a patient with proved amebic pericarditis secondary to a hepatic abscess Their patient was treated with open drainage of the pericardium Purcell,<sup>3</sup> as well as Laigret,<sup>4</sup> reported a case of amebic abscess of the liver with signs of pericardial effusion Their patients recovered under treatment with emetine hydrochloride, but the nature of the pericardial fluid was not determined It is probable that in these 2 cases only a serous pericardial effusion existed, such an effusion was noted in 6 of the 150 cases of abscess of the liver reported by Huard and Meyer-May

#### SUMMARY

In a case of amebic pericarditis subsequent to extension of an amebic abscess of the liver, the clinical impression was that of tuberculous pericarditis, and the diagnosis was established only at autopsy

<sup>3</sup> Purcell, F. M. Case of Amoebic Hepatic Abscess and Associated Pericarditis, *Tr. Roy. Soc. Trop. Med. & Hyg.* **31**: 689 (April) 1938

<sup>4</sup> Laigret, L. Pericardite au cours d'une dysenterie amibienne, *Bull. Soc. path. exot.* **21**: 753, 1928

# ULCERATIVE TRACHEOBRONCHITIS FOLLOWING ATYPICAL PNEUMONIA

## REPORT OF CASES

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It is no longer felt that atypical (viral) pneumonia is always as innocuous as it was originally described. Many patients have experienced recurring episodes of this disease over a period of several years. In some the symptoms have continued unabated, a productive cough has developed, and the presence of bronchiectasis has been confirmed by bronchographic examination. Other patients have had residual ulcerative tracheobronchitis associated with hemoptysis and production of sputum. These patients may show roentgenographic evidence of bronchial and bronchiolar dilatation and occlusion, atelectasis or obstructive emphysema. In others the convalescence has been prolonged and characterized by neurasthenia, chronic cough, production of sputum, pain in the chest, generalized weakness, easy fatigability, occasional hemoptysis, loss of weight or failure to regain previous weight lost, elevated sedimentation rate and low grade fever.

Twenty-nine of 150 patients having bronchoscopic examinations during the first six months of 1944 were found to have ulcerative lesions of the tracheobronchial tree. Nine of these patients had previous episodes of atypical pneumonia. Of the others, 6 had the lesions secondary to tuberculosis, 4 had them secondary to bronchiectasis, and in 3 they were associated with pulmonary abscesses. One had blastomycosis and 1 Boeck's sarcoid, and for 5 the cause of the lesions could not be determined. It is with the 9 patients whose ulcerative tracheobronchitis appeared to be secondary to previous attacks of atypical pneumonia that this paper is primarily concerned.

Atypical pneumonia is generally believed to be due to viral infection, though many pathogenic agents have been shown clinically and roentgenologically to be capable of producing this disease picture. Because of the difficulty in performing viral studies, the diagnosis must usually be made by exclusion, based primarily on the clinical course and the roentgenographic characteristics

after the other etiologic agents have been eliminated.

Atypical pneumonia in its mild form has been frequently described.<sup>1</sup> Lately, other observers<sup>2</sup> have described a more severe, protracted and recurrent form of the disease occurring along with the milder forms in the same epidemic. The course may be longer, persisting in some in-

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stances for months and occasionally being followed by complications. Van Ravenswaay and his associates<sup>2a</sup> have stressed the virulent aspect of this disease. Twenty-three and three-tenths per cent of their patients allowed to get up too soon had a recurrence of the pneumonia, and an additional 18.5 per cent had other complications, such as pleural fluid, empyema, chronic bronchitis and bronchiectasis. In my series there have been 20 patients in whom bronchiectasis developed after atypical pneumonia, 11 have had empyemas, and 9 have had residual ulcerative tracheobronchitis. Many others have had a delayed convalescence, characterized by neurasthenia, loss of weight, easy fatigability and chronic bronchitis. It is impossible to determine the general incidence of complications, for most patients were transferred to this hospital after the complications developed.

In a previous report<sup>3</sup> it was shown that atypical pneumonia may cause bronchial and bronchiolar infection and occlusion. The bronchial occlusion, manifested by areas of atelectasis, was demonstrated bronchoscopically by swollen, edematous and ulcerated mucous membrane, as well as by plugs of purulent exudate. Although ulcerations of the tracheobronchial tree have been shown microscopically in patients who died of atypical pneumonia, it is not generally realized in clinical practice that atypical pneumonia may be associated with or followed by ulcerative tracheobronchitis, recognizable bronchoscopically. This condition may account for the delayed convalescence, the symptoms of chronic bronchitis and hemoptysis and the recurring episodes of the disease noted in many patients. Roentgenologically, evidence of bronchiectasis, atelectasis or obstructive emphysema may be noted, depending on the duration, severity and degree of healing of the disease process. For other patients the roentgenogram of the chest may be normal.

Bronchoscopic examination of a patient with atypical pneumonia by Clerf, as reported by Reimann, showed diffuse inflammation of the entire tracheobronchial tree, particularly of the bronchus of the lower lobe of the left lung, which contained tenacious exudate. Dingle and his associates<sup>1b</sup> described the bronchoscopic observations in 10 patients with atypical pneumonia. There was an acute inflammatory reaction of the bronchial mucosa, with considerable congestion. The secretion was mucoid to mucopurulent. According to Blades and Dugan,<sup>4</sup> the appearance

of the bronchial tree in a person with pseudo-bronchiectasis after atypical pneumonia is characterized by an extremely edematous mucous membrane, with a generalized inflammatory reaction which might be described grossly as suppurative bronchitis. It has not been my privilege to perform bronchoscopic examinations on many patients during the initial acute episode of atypical pneumonia. Those who have been so examined have shown diffuse inflammation of the mucous membrane, involving the larynx, trachea and both bronchial trees. The majority of patients with ulcerative tracheobronchitis have been transferred to this hospital several months after the onset of the disease and occasionally as long as six months to a year and a half afterward.

Bronchoscopic examination of patients with ulcerative tracheobronchitis following atypical pneumonia reveals the mucous membrane of the larynx, trachea and both bronchial trees to be severely inflamed and irritated. If the process is relatively acute, the mucous membrane is easily traumatized. The ulcerations are usually multiple and may be bilateral. The posterior and posterolateral walls are the sites usually involved, but the anterior wall may also be involved to a lesser extent. The ulcerations simulate the "tear drop" ulcer commonly found in tuberculosis, for which they could easily be mistaken. Occasionally the edges of the ulcer are ragged and hyperplastic. This hyperplasia could cause bronchial occlusion and atelectasis if the ulcer were located near a bronchial orifice. Usually, however, the borders of the ulcers are smooth, with only a little overhanging edge. The ulcers may be covered by a thin transparent grayish yellow membrane. Cultures of materials taken from such ulcers have not contributed to the diagnosis, only the usual bacterial flora being obtained. Facilities have not allowed viral studies. Biopsy of the ulcers and surrounding tissues has revealed nonspecific granulation tissue and inflammation. If the process is of long duration, it may be associated with scarring and stenosis of the secondary bronchial orifices, giving rise to obstructive emphysema and atelectasis. The ulcers are readily cauterized with 30 per cent solution of silver nitrate, whereas the intervening mucous membrane remains unchanged. The ulcerations tend to remain chronic and resistant to therapy. Healing usually takes place within a period of two to four months.

*Diagnosis*—The diagnosis depends on the detection of ulcerations in the tracheobronchial tree in a patient who has or has had atypical pneumonia and residual symptoms therefrom. The patient may have a chronic productive bron-

3 Kay, E. B. Bronchiectasis Following Atypical Pneumonia, *Arch Int Med* 75:89-104 (Feb) 1945.

4 Blades, B., and Dugan, D. J. Pseudo Bronchiectasis Following Atypical Pneumonia, *Bull U S Army M Dept*, November 1943, no. 70, pp. 60-68.

chitis with hemoptysis and recurrent episodes of pneumonitis or nonresolution of pneumonitis with roentgenographic or bronchographic evidence of bronchial or bronchiolar damage. Since it is frequently impossible to make a positive diagnosis as to the cause of the ulcers because of the difficulty in performing viral studies, this diagnosis must remain a clinical one, made after other etiologic agents capable of producing tracheobronchial ulcerations have been thor-

tive granulomas, particularly to tuberculous granulomas, have been the most difficult to differentiate bronchoscopically.

*Differential Diagnosis*—Ulcerative tracheobronchitis associated with atypical (viral) pneumonia may be indistinguishable bronchoscopically from similar superficial ulcerations due to Boeck's sarcoid (fig 1 *A*), from the chronic infective granulomas (fig 1 *B*) or from the bronchomycoses (fig 1 *C*). Bacteriologic and path-

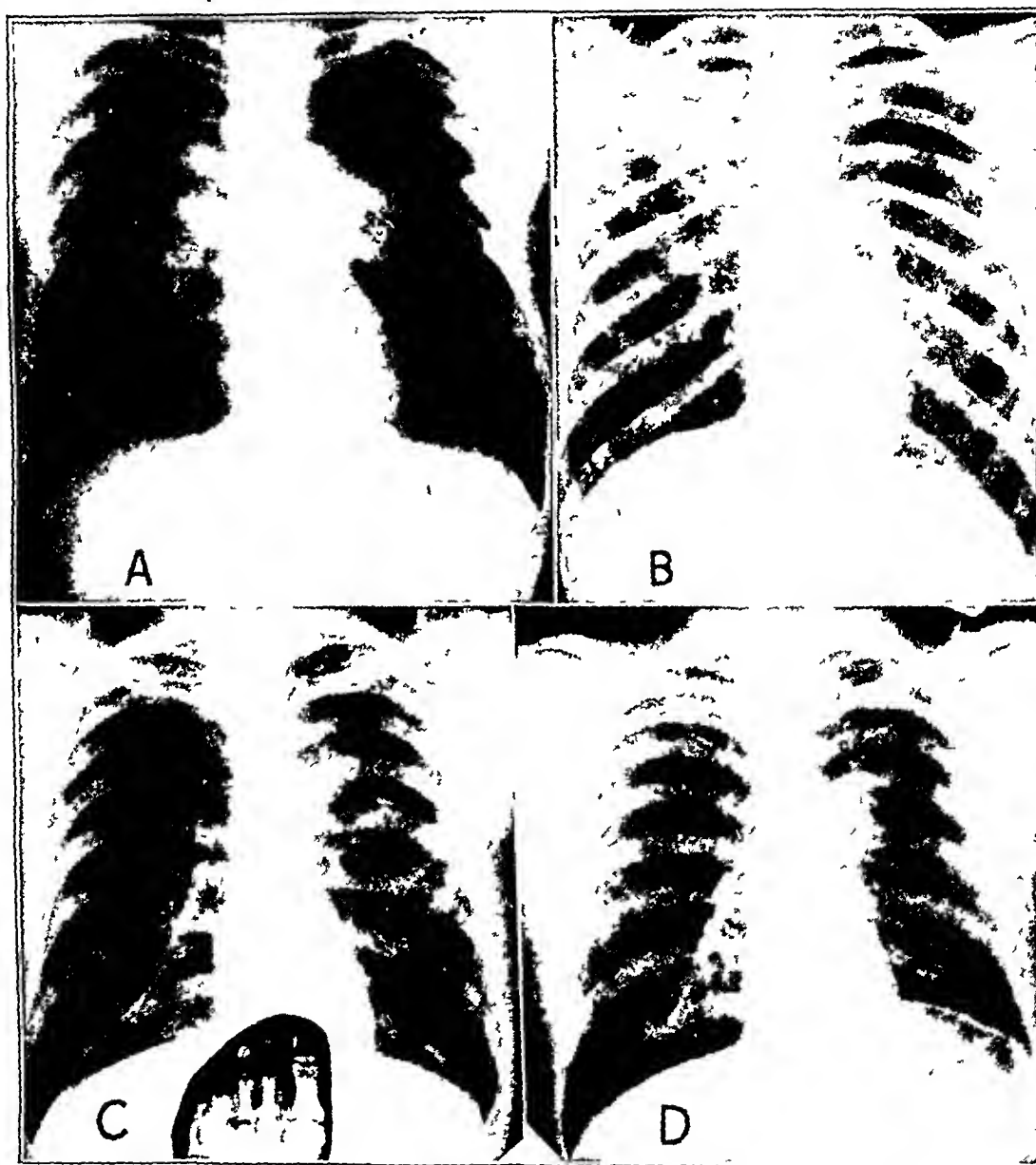


Fig 1—Roentgenograms of patients with other bronchopulmonary diseases who also had ulcerative lesions of the bronchi simulating those seen bronchoscopically in atypical pneumonia. *A*, involvement of the pulmonary and hilar lymph nodes seen in Boeck's sarcoid. There was pathologic verification of the diagnosis by examination of the lymph nodes by biopsy and by bronchoscopic biopsy. *B*, pulmonary tuberculosis of the apex of the right lung; acid-fast tubercle bacilli were obtained from the sputum. *C* and *D*, pulmonary and osseous involvement resulting from blastomycosis; *D* illustrates the appearance of the chest six months after *C* was taken, showing the definite improvement. The patient had a temporary interruption of the left phrenic nerve and removal of the fourth metatarsal bone and the proximal phalanx. He was given sulfonamide drugs for three months and was discharged clinically well.

oughly investigated and excluded. So far, cultures of intrabronchial materials and biopsy have not aided. High titers of cold agglutinins in the serum have been of presumptive value. Tracheobronchial ulcerations secondary to chronic infec-

tive investigation in these diseases, however, has usually proved the cause. Early or superficial ulcerative tuberculous tracheobronchitis most closely simulates this condition bronchoscopically, although it tends to be even more

chronic and resistant to therapy. Careful search for the tubercle bacillus by repeated cultures and inoculations in guinea pigs of sputum and gastric washings results in a positive diagnosis for a high percentage of tuberculous patients. The nonspecific inflammations and pyogenic ulcerations associated with bronchiectasis and pulmonary abscesses can readily be differentiated by the clinical course of these diseases.

*Treatment*—A general hygienic regimen is followed. The patient is given complete rest in

secondary bronchi are sponged with tetracaine and epinephrine hydrochlorides solution to improve drainage and the ulcerations are cauterized with 30 per cent silver nitrate. The daily instillation of 3 to 5 cc of penicillin (250 units to the cubic centimeter) into the tracheobronchial tree was thought to be of definite value in promoting more rapid healing. In subsequent cases, the concentration of penicillin has been increased to 10,000 units to the cubic centimeter, with evidence of further benefit. After a period of approximately

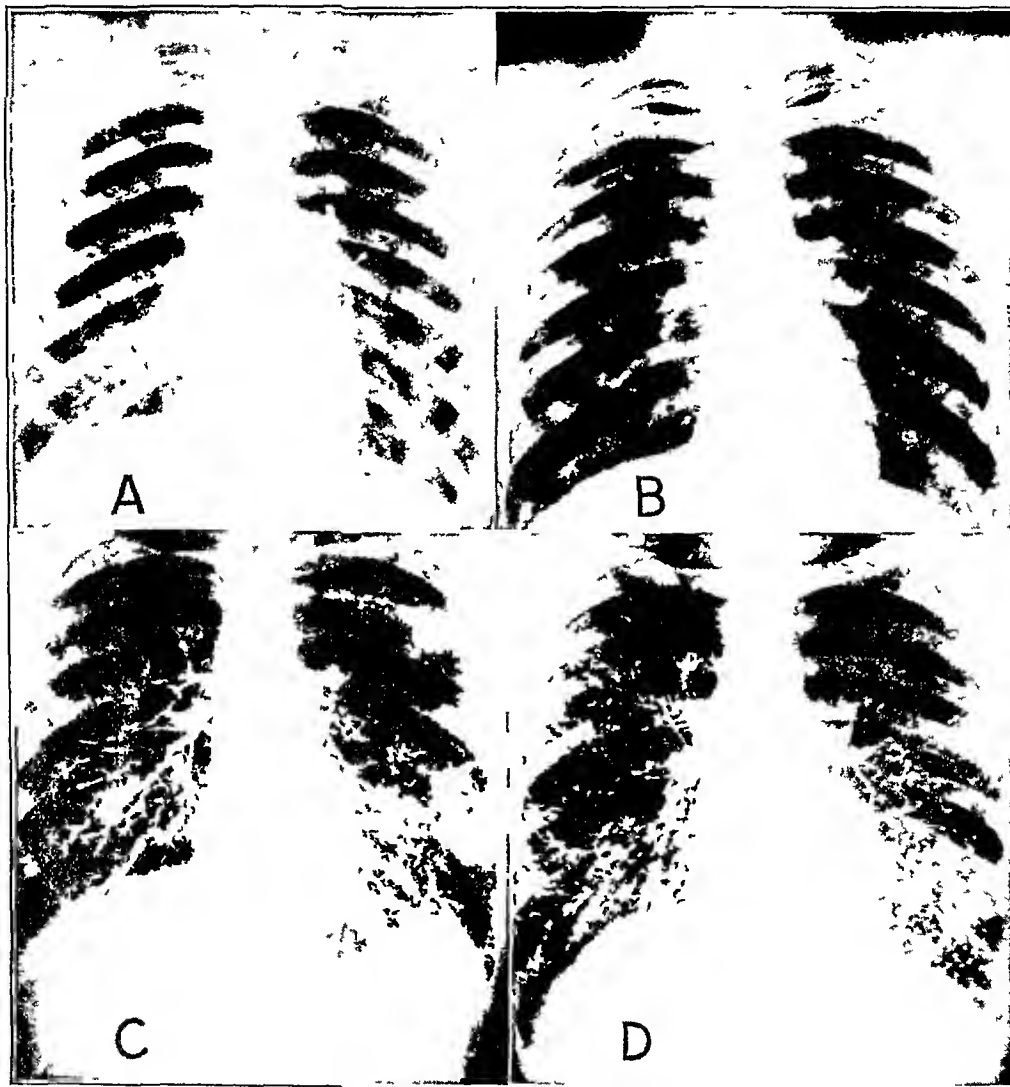


Fig 2 (case 1)—Roentgenograms of a patient with recurring attacks of atypical (viral) pneumonia, ulcerative bronchitis and cylindric bronchiectasis of the lower lobe of the left lung. *A*, roentgenographic evidence of pneumonitis in the lower field of the right lung during the initial attack of atypical pneumonia Jan 18, 1943. *B*, roentgenographic evidence of pneumonitis in the lower field of the left lung during a recurrent episode of atypical pneumonia Jan 4, 1944. *C*, bronchogram made June 4, demonstrating minimal cylindric bronchiectasis in the lower lobe of the left lung. *D*, bronchogram made August 8, demonstrating no appreciable improvement in the bronchial dilatation even though there was considerable improvement in the ulcerative bronchitis shown bronchoscopically.

bed except for bathroom privileges, a high vitamin, high caloric diet and inhalations of steam or benzoin. If there is a productive cough, postural drainage is employed. The patient is examined bronchoscopically every four weeks, at which times the bronchial orifices of the sec-

one or two months of this regimen, the patient usually gains weight, the cough decreases or disappears, and a sense of well-being is noted. When the lesions appear bronchoscopically to be healing and the sedimentation rate becomes or remains normal, the patient is gradually allowed

more activity but continues to have midmorning and midafternoon rest periods until complete healing has taken place. The ulcerations are usually healed within two to four months.

#### REPORT OF CASES

Only 4 reports of cases will be presented. These are characteristic of the group as a whole and illustrate the various clinical, roentgenographic and bronchoscopic aspects of the disease. All of the patients in these cases had two to four previous episodes of atypical pneumonia, which were all followed by chronic productive bronchitis and general debility. Three patients noted hemoptyses. The first case report illustrates migratory atypical pneumonia followed by bilateral ulcerative tracheobronchitis and bronchographic evidence of cylindric bronchial dilatation. The second is similar but emphasizes atelectasis. The third describes the complications of bronchostenosis and obstructive emphysema. The fourth demonstrates ulcerative bronchitis with no roentgenographic evidence of pulmonary residua.

**CASE 1**—The patient, a 20 year old white youth, complained of a constant productive cough, loss of weight and nervousness. The past history was noncontributory. During childhood he had had scarlet fever, mumps, measles, whooping cough and chickenpox. The patient's health prior to his induction into the army was good. Two weeks after induction, Jan 18, 1943, he contracted atypical pneumonia in the lower lobe of the right lung, characterized by chills, a temperature of 104 F, a productive cough and substernal pain. The white blood cell count was normal, and examination of the sputum showed only the normal flora. Physical examination revealed nasopharyngitis and rales in the right lower pulmonary field posteriorly. There was roentgenographic evidence of basilar pneumonitis on the right side (fig 2A). The temperature was normal in five days, but the cough, sputum and general weakness persisted.

After eight weeks' hospitalization the patient was discharged to duty. He continued to have a cough and to raise sputum, but the symptoms were not sufficient to require his hospitalization. On October 29 the patient was rehospitalized for bilateral basilar pneumonitis, demonstrated by clinical and roentgenographic examination. The productive cough and substernal pain increased. His temperature at this time never went over 101 F. The sedimentation rate was 22 mm in sixty minutes, and the white blood cell count was 6,100. The rales disappeared after three days, and within twelve days the chest was clear roentgenologically.

After four more weeks the patient was again returned to duty. The cough, sputum and general weakness continued. On Jan 4, 1944, the patient again experienced an increase in the cough and sputum and complained of pain in the left side of his chest and was rehospitalized. The temperature was 103.4 F, the white blood cell count 7,800 and the sedimentation rate 26 mm in sixty minutes. The throat was injected, and there were numerous coarse rales throughout the lower posterior field of the left lung. Roentgenograms showed pneumonia in the left base (fig 2B). By January the pulmonary fields were again clear. He returned to duty March 23.

In May there was a fourth recurrence of the pneumonia, as before in the lower fields of the left lung, and he was transferred to Percy Jones General Hospital. Physical examination revealed moist rales throughout both pulmonary fields, more predominant on the left side. The patient showed evidence of loss of weight and general debility. There was a low grade elevation of temperature, up to 99.4 F, daily. The patient complained of substernal pain and pain throughout both sides of his chest. He had a persistent cough and raised between 20 and 30 cc of purulent sputum daily. Smear, culture and inoculations in guinea pigs showed no growth of tubercle bacilli but did grow hemolytic streptococci and nonhemolytic *Staphylococcus aureus*. The white blood cell count was 6,600 and the sedimentation rate 29 mm in sixty minutes. Cold agglutinins were present in a titer of 1 to 128. Because of the suggestive evidence of bronchiectasis, a bronchogram was made June 4, which showed cylindric bronchiectasis in the lower lobe of the left lung and several areas of bronchial dilatation in the lower lobe of the right lung, as demonstrated in figure 2C. Bronchoscopic examination on June 27 showed diffuse inflammatory hyperemia of the larynx, trachea and both main bronchi. Throughout the entire left main bronchus and, to a lesser extent, in the right main bronchus were multiple areas of superficial ulcerations, some of which had the "tear drop" appearance while others appeared shaggy and hyperplastic.

The ulcerations were thoroughly cauterized with 30 per cent silver nitrate solution. After this procedure the patient was treated as outlined in the section on treatment. The cough gradually decreased, as well as the production of sputum. The sedimentation rate by August 8 had decreased to 7 mm in one hour. Rales persisted throughout both pulmonary fields, predominantly on the left, until August 1. Bronchoscopic examination August 21 showed definite improvement in the degree and extent of the ulcerative tracheobronchitis, that on the right side being almost entirely healed and that on the left side considerably improved. Bronchographic examination August 8 (fig 2D) showed no significant improvement of the cylindric bronchial dilatation.

A gain in weight and a sense of well-being have been noted. The productive cough is noticeably improved but is occasionally present. The sputum now does not exceed 5 cc in amount daily.

**CASE 2**—The patient, a 51 year old officer, was hospitalized elsewhere for two weeks in November 1943 for an infection of the upper respiratory tract. The past history was entirely noncontributory. There were few symptoms referable to the lungs. A roentgenogram of the chest taken November 9 showed massive atelectasis of the lower lobe of the right lung, with an elevated diaphragm and mediastinal shift. By November 16 there had been spontaneous clearing of the lobar atelectasis. It was felt that the patient had had a mild attack of atypical pneumonia.

The patient was returned to duty and felt entirely well until December 19, at which time a productive cough developed and he was again hospitalized. There were 4 or 5 ounces (120 or 150 cc) of purulent sputum daily. The temperature was elevated to 104 F for four days and gradually fell by lysis. Atelectasis of the lower lobe of the right lung was again noted (fig 3A), and a new pneumonic process had developed in the base of the left lung. Also, there was an increase in the obliterative pleuritis, resulting in elevation and flattening of the left side of the diaphragm. Within a week, as before, there was spontaneous clearing of the atelectasis, but the process in the lower lobe of the left lung persisted for

the next month (fig 3 *B*), associated with basilar rales on this side. The productive cough disappeared.

The patient was then transferred to Percy Jones General Hospital. Bronchoscopic examination performed Jan 24, 1944, showed erythematous granular mucous membrane with several small superficial areas of ulceration in the bronchus of the lower lobe of the left lung, while the bronchus of the lower lobe of the right lung showed extensive ulceration of an acute nature, with some diminution of the bronchial lumen. The bronchial ulcerations were thoroughly cauterized with 30 per cent silver nitrate solution. Because of the suggestive evidence of bronchiectasis, bronchographic examination was performed January 31, and damaged, dilated and somewhat distorted bronchi and bronchioli were noted in the bronchograms (fig 3 *C*). The patient was treated according to the procedure previously out-

characterized by fever, cough and generalized weakness of two days' duration. The past history was non-contributory. His temperature on his admission to the hospital was 103.4 F. The white blood cell count was 5,000, with a differential count of 65 per cent polymorphonuclear leukocytes, 27 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. The patient appeared extremely ill and was dyspneic, and rales could be heard in the right lower pulmonary fields posteriorly. A roentgenogram revealed pneumonic infiltration at the base of the right lung. Treatment with sulfadiazine was started immediately but was discontinued after three days because of no alleviation of the fever.

By March 3 there were rales throughout both pulmonary fields. Roentgenographic examination at this time showed patchy areas of pneumonitis throughout the right lung and in the left hilar region (fig 4 *A*).

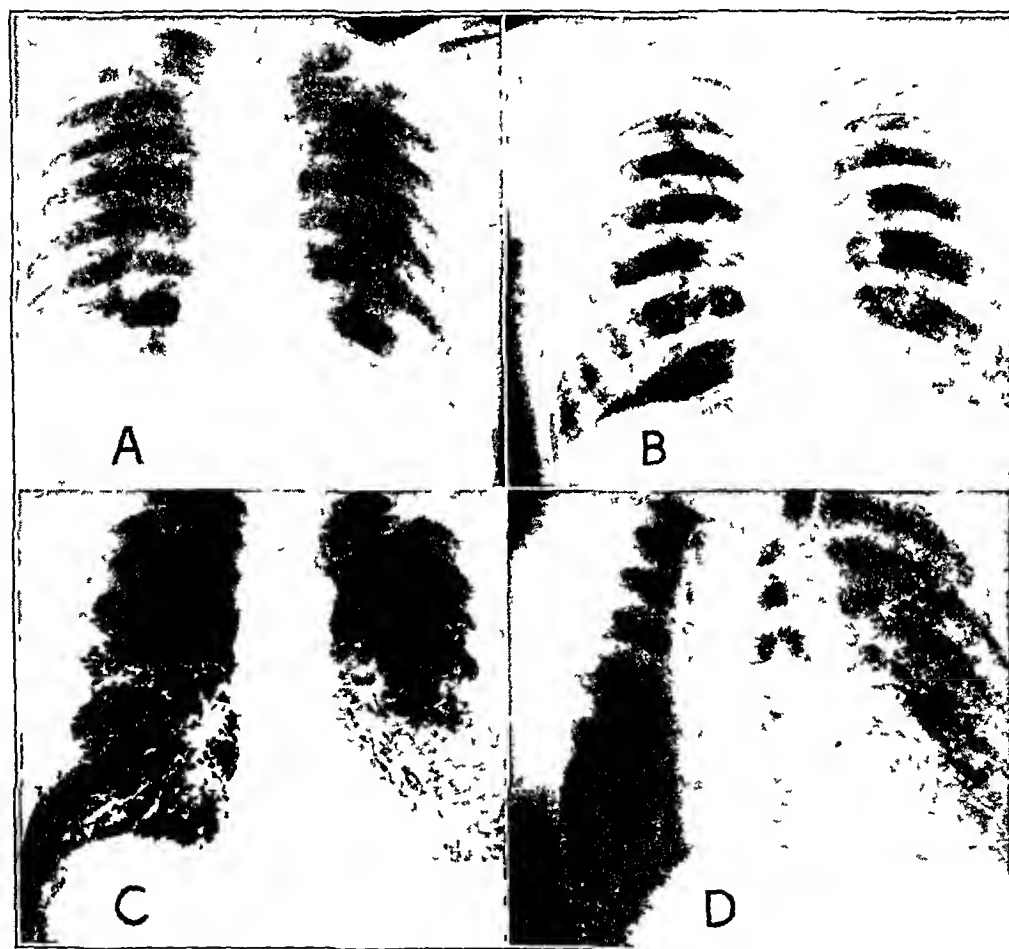


Fig 3 (case 2)—Roentgenograms of a patient who had two attacks of atypical pneumonia associated with ulcerative bronchitis, atelectasis of the lower lobe of the right lung and residual bronchial damage of the lower lobe of the left lung. *A*, evidence of the elevated right side of the diaphragm associated with atelectasis in the base of the right lung and pneumonitis in the base of the left lung Dec 19, 1943; *B*, roentgenogram made December 26, demonstrating spontaneous clearing of the atelectasis of the lower lobe of the right lung but some increase in the pneumonitis in the left lower pulmonary field; *C*, bronchogram made Jan 31, 1944, demonstrating dilated and distorted bronchi of the lower lobe of the left lung; *D*, bronchogram made March 21, demonstrating slight increase in the bronchial dilatation. The ulcerative bronchitis appeared bronchoscopically to be healed at this time.

lined. A second bronchoscopic examination, on March 11, showed complete healing of the previous ulcerative bronchitis. However, bronchographic examination March 21 (fig 3 *D*) showed a slight increase in the bronchial dilatation.

Additional bronchograms obtained later showed this process to be stationary.

CASE 3—The patient, a 25 year old man, was hospitalized elsewhere Feb 17, 1943, for atypical pneumonia,

Dyspnea and cyanosis were so severe as to require oxygen therapy. There was only a moderate amount of sputum, and this was negative for pathogenic organisms, including tubercle bacilli. There was hemoptysis on one occasion. Clinical and roentgenographic examination of the chest showed clearing of the multiple areas of pneumonia, except for those in the base of the right lung, by April 19 (fig 4 *B*), and these were clear by May 6.

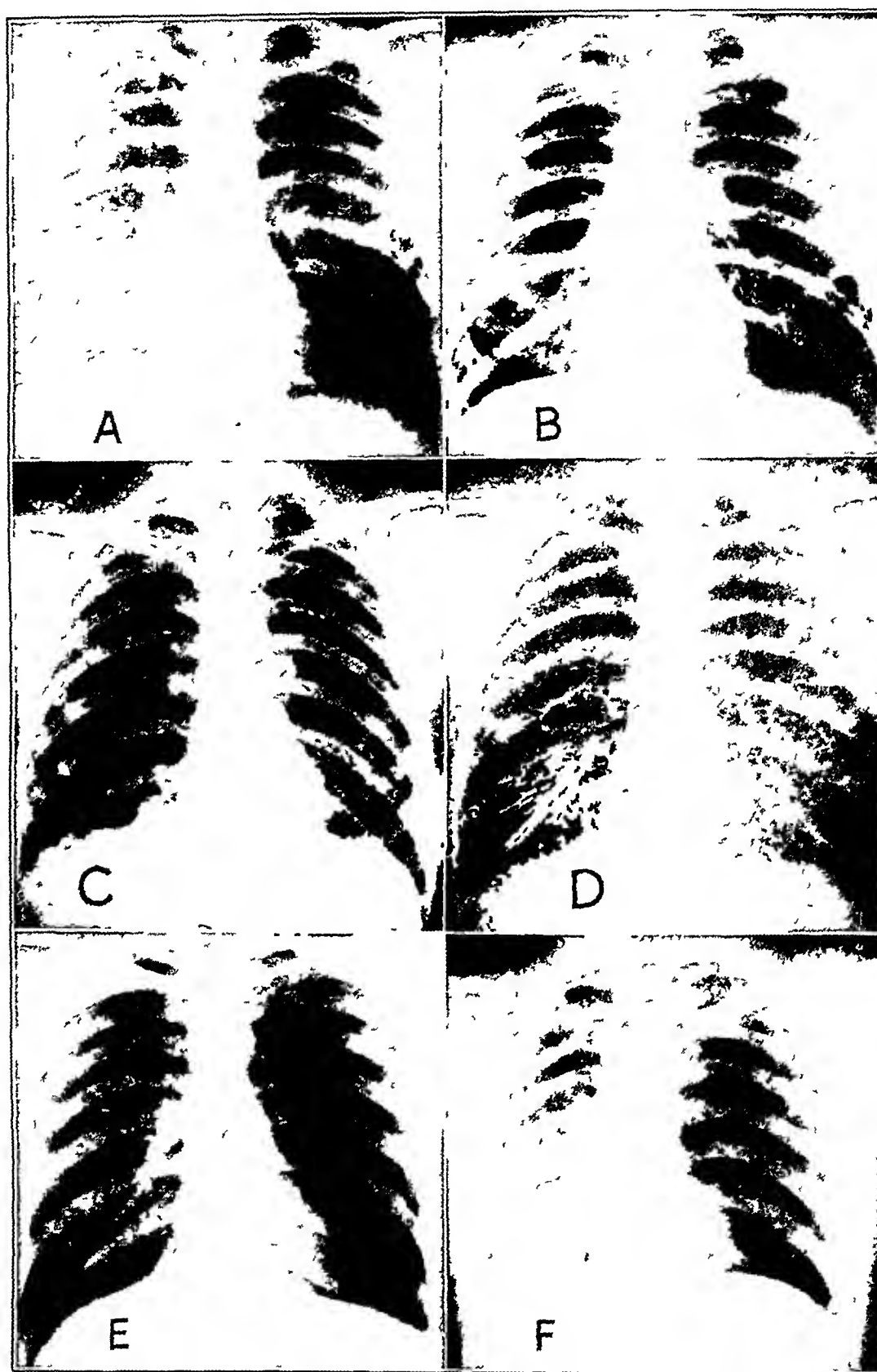


Fig 4 (case 3) —Roentgenograms of a patient with recurring attacks of atypical pneumonia, bronchoscopic evidence of ulcerative tracheobronchitis, with multiple sites of bronchostenosis on the right side and residual obstructive emphysema of the right lung *A*, roentgenographic evidence of bilateral pneumonitis during the initial episode of atypical pneumonia March 3, 1943, mediastinal shift to the right side is noted *B*, roentgenogram made April 19, showing clearing of the bilateral pneumonitis except in the base of the right lung. Mediastinal shift to this side is still present *C*, roentgenogram taken Jan 18, 1944, showing evidence of emphysema of the right lung *D*, bronchogram taken April 15, demonstrating generalized tubular dilatation of the smaller bronchi of the right lung, with apparent occlusion of the terminal ends proximal to the emphysema, this was interpreted to be due to inflammation, mucous plugs or scarring and resulted in a ball valve mechanism accounting for the emphysema *E* and *F*, roentgenograms demonstrating obstructive emphysema of the left lung in another patient having ulcerative bronchitis with multiple sites of bronchostenosis, as did the patient whose bronchogram is shown in *D*, but no definite evidence of previous attacks of atypical pneumonia

The patient then returned to duty but noted a chronic moderately productive cough and weakness. On July 26 he was again hospitalized for a productive cough, dyspnea on exertion and pain in the right aspect of the chest. Physical examination showed diminished breath sounds and resonance over the entire right aspect of the chest and the presence of a friction rub in the right axilla. The blood count was normal, as was the roentgenogram of the chest. After several weeks he again returned to duty and remained moderately well except for the productive cough, dyspnea and weakness.

On Jan 18, 1944, the patient was again hospitalized for what was diagnosed as a "cold" and fever of two days' duration. Roentgenograms at this time revealed emphysema of the right lung (fig 4 C). Physical examination revealed rales throughout the right pulmonary field and the presence of diminished breath sounds and hyper-resonance in the same area. Bronchograms (fig 4D) revealed generalized dilatation of the smaller bronchi on the right side with apparent occlusion of the terminal ends. This prevented the iodized poppyseed oil from entering the distal bronchioles and alveoli. Those that did fill appeared emphysematous. The occlusion of the terminal ends of the bronchi was presumed to be due to inflammation, mucous plugs or scarring. Apparently a ball valve mechanism had resulted from the disease process. A diagnosis of emphysema of the middle and lower lobes of the right lung secondary to atypical pneumonia was made, and the patient was then transferred to Percy Jones General Hospital.

Physical examination showed the same conditions as those just described. Because of the previous history of atypical pneumonia followed by a productive cough and evidence of emphysema, bronchoscopic examination was done May 19. This showed considerable tenacious mucous exudate in the right main bronchus and about the bronchial orifices, the surfaces of the mucous membranes were hyperemic and inflamed. There were multiple superficial ulcerations on the posterior and posterolateral walls, extending from 1 to 2 cm below the bronchus of the upper lobe of the right lung down to the secondary bronchial orifices of the lower lobe of the right lung. There was definite partial stenosis of the orifices of the bronchi of the secondary, mediastinal, vertebral and dorsal lobe, as well as of the bronchus of the middle lobe. These bronchial orifices varied from approximately the size of a pinpoint to 2 mm in diameter.

All of the sites of bronchostenoses were dilated, and the ulcers were cauterized. The patient was given the general treatment described previously. A second bronchoscopic examination, done a month later, showed some healing of the bronchial ulcerations, but the sites of the bronchostenoses had again returned to their previous caliber. During the interim there was some decrease in the cough and the production of sputum but no apparent change in the roentgenographic and clinical evidence of emphysema. The patient was discharged from the army before further therapy could be carried out.

Figures 4 E and 4 F show the roentgenograms of another patient who had more pronounced evidence of obstructive emphysema and also bronchoscopic evidence of ulcerative bronchitis and multiple sites of bronchostenosis of the secondary bronchi similar to those of the patient described.

CASE 4—The patient, a 36 year old medical officer, was admitted to Percy Jones General Hospital July 21, 1944, with the history of bilateral atypical pneumonia in 1941 which had the typical roentgenographic appearance and clinical course. This had cleared after four to six weeks without residua. In childhood the patient had had mumps, smallpox, chickenpox and whooping cough. He remained healthy until April 1944, at which time he was hospitalized for a "chest cold" associated with chills, a temperature of 101.4, headache and pain in the right side of the chest and the sub-sternal areas. Physical examination revealed nasopharyngitis and evidence of rales in the right pulmonary field in the posterior axillary line at the level of the seventh and eighth ribs. Roentgenograms of the chest showed nothing abnormal.

In forty-eight hours the rales had disappeared, the patient felt well, and he was discharged to duty. Within three days a sore throat, cough, sputum and a low grade fever again developed. He was hospitalized for one week, during which time thorough examinations of the sputum for pyogenic organisms, tubercle bacilli and coccidioides were made without result.

On June 2 the patient was again hospitalized for chills, a temperature of 101.4 and pain in the right side of the chest. Examination of the chest revealed coarse rales throughout both pulmonary fields. Within two days the temperature was again normal and the patient felt better, but a productive cough developed that was associated with hemoptysis on three or four occasions. Roentgenograms of the chest showed evidence of pneumonitis in the right cardiophrenic angle of the right pulmonary field. This gradually disappeared over two weeks' time, but rales persisted posteriorly and laterally in the right pulmonary field. The white blood cell count was 4,500, and the sedimentation rate was 31 mm in one hour. Examination of the sputum again showed no significant organisms.

The patient was then transferred to Percy Jones Hospital. There was definite evidence of chronic illness, characterized by general debility, nervousness, a productive cough and hoarseness. The pharynx was injected. Examination of the chest again revealed the presence of inspiratory rales in the right pulmonary field posterolaterally. Roentgenograms of the chest were normal. Because of the previous experience of finding ulcerative tracheobronchitis following atypical pneumonia, a bronchoscopic examination was done July 27. An inflamed, irritated mucous surface of the larynx, trachea and both bronchial trees was noted. Beginning at the carina on the right side were extensive ulcerations throughout the entire right main bronchus. The ulcerations were moderately deep, with a slightly overhanging edge. Some appeared red, while others were covered with a transparent yellowish membrane.

The ulcers were examined by culture and biopsy and were cauterized with 30 per cent silver nitrate solution. No pathogenic organisms were grown on culture. Facilities were not available for viral studies. The microscopic examination of the tissue showed only nonspecific inflammation. Extensive studies for both tuberculosis and fungous infections were done without result. The white blood cell count remained normal, but the sedimentation rate decreased to 7 mm in sixty minutes. There was no evidence of cold agglutination. The patient was given rest in bed for a month, a high vitamin, high caloric diet with supplementary

vitamins and frequent steam inhalations. Daily intratracheal instillation of penicillin was done. The patient gradually improved, the cough, sputum and hoarseness disappeared, and there was an increase in appetite and a gain of 10 pounds (4.5 Kg) in weight.

On September 3 a second bronchoscopic examination was done, which showed normal-appearing mucous membrane of the larynx, trachea and bronchi. There was practically complete healing of the ulcerative bronchitis except for one small patch, approximately 12 by 4 mm, on the left posterolateral wall of the right main bronchus.

#### SUMMARY

Atypical (viral) pneumonia in its more protracted and recurrent form was studied. This

disease may be complicated by bronchiectasis, empyema, ulcerative tracheobronchitis and delayed convalescence. Patients with atypical pneumonia may have ulcerative lesions in the tracheobronchial tree, and these may be responsible for the protracted and recurrent forms of this disease. Bronchoscopic examination is indicated in the management of such patients, for both diagnosis and local therapy. General hygienic therapeutic measures directed to the patient are important. It is felt that the daily instillation of penicillin intratracheally has been of value in promoting more rapid healing of the tracheobronchial ulcerations.

# EPIDEMIC HEPATITIS WITH AND WITHOUT JAUNDICE

SOME CLINICAL STUDIES ON TWO HUNDRED AND FIFTY-FIVE PATIENTS  
AMONG TROOPS IN A COMBAT ZONE

MAJOR ROBERT M FINKS AND CAPTAIN RICHARD W BLUMBERG

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In almost every war during the last one hundred and fifty years increased numbers of cases of jaundice have been observed among soldiers. According to a report in The Bulletin of the U S Army Medical Department,<sup>1</sup> "There were 22,569 cases and 161 deaths during the Civil War in a total of 2,218,559 troops, the disease occurred in troops during the Boer War, the War of 1812, the Spanish-American War, and World War I." Similar outbreaks were experienced by British troops in the Middle East in 1941 and 1942. During the late summer and fall of 1943 an epidemic of infectious hepatitis began among American, British and French troops in the North African theater. Admissions to the hospital for jaundice in this theater, which included Sicily and Italy, began to increase in August and September, reached a peak during the winter months and then began to decline. This increasing incidence of hepatitis presented an unusual opportunity to study the clinical characteristics of a large number of these cases and to compare them with those seen in various other types of jaundice.

## METHODS AND MATERIAL

During the six month period from Nov 16, 1943 to May 16, 1944, a total of 448 patients with jaundice were admitted to the gastroenterologic service of a general hospital located in Italy. Many additional patients were admitted to other medical wards, or jaundice developed in patients in the surgical wards, hence this figure is not a true index of the number of patients admitted to this hospital during this period.

Of this total, 196 patients with hepatitis and jaundice uncomplicated by other diseases and 42 patients having additional diseases simultaneously were studied by means of various clinical and laboratory tests. This report is based on our observations of this group of 238 unselected patients with hepatitis and jaundice. In addition to these, 17 patients with hepatitis without jaundice were observed and similarly studied.

Because of the large number of patients under observation during a relatively short period, specimens of varying size were studied by different clinical and laboratory tests. In addition to a careful clinical history and physical examination, we studied some patients by weekly determinations of the icterus index, van den

Bergh reaction, urinalysis, bile content of the stools and complete blood counts. Various special studies, such as the hippuric acid test of hepatic function according to the gravimetric method of Quick,<sup>2</sup> the sedimentation rate according to the method of Wintrobe and Landsberg,<sup>3</sup> the coagulation time by the capillary tube method,<sup>4</sup> the heterophile agglutination test and the dark field examination of blood and urine for leptospiras and spirochetes, were performed on a variable but significant number of patients. Examinations of urine and stools for bile were frequently made throughout the course of the disease on all patients. Each was frequently examined for any changes in physical conditions, with particular emphasis on the degree of icterus, lymphadenopathy, hepatic tenderness or enlargement and splenomegaly.

Those studied were patients with hepatitis consecutively admitted and unselected except that for purposes of study an icterus index of at least 16 was arbitrarily set as the lower limit indicating the presence of jaundice. A large number of patients with milder forms of the disease were thus excluded, but in the cases reported the diagnosis of epidemic hepatitis with jaundice has been unquestionably verified.

## CLINICAL DATA

*Age, Race and Sex*—The average age of the 101 patients was 23.9 years, the youngest being 19 and the oldest 38. All were white men. There were no Negroes in this series. Since the ratio of Negro troops to white troops in this theater is unknown, no conclusion as to this apparent racial immunity can be drawn. There were only 2 women admitted to this hospital with jaundice during the six month period of this study, however, less than 1 per cent of the patients admitted to the hospital during this period were women.

*Incubation Period*—No accurate estimation of the incubation period could be made because of the lack of any history of known contacts for 28 per cent of the patients and because of the

2 Quick, A. J. The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am J M Sc* **185** 630 (May) 1933.

3 Wintrobe, M. M., and Landsberg, J. W. A Standardized Technique for the Blood Sedimentation Test, *Am J M Sc* **189** 102 (Jan) 1935.

4 Methods for Laboratory Technicians, U S War Department, Technical Manual 8-227, Washington, D C, Government Printing Office, Oct 17, 1941, p 28.

1 Epidemic Hepatitis. A War Disease, *Bull U S Army M Dept* November 1943, no 70, p 4.

extremely wide range of multiple contacts for the remaining 72 per cent. Cameron,<sup>5</sup> in his studies on 170 patients with epidemic hepatitis observed in Palestine in 1940 and 1941, stated the belief that the minimum incubation period was thirty-two days and in many cases much longer. We have not been able to add further information in regard to the incubation period.

For convenience of description we have separated the disease into three phases: preicteric, icteric and convalescent phases, and each will be discussed in detail.

*Preicteric Stage*—These data were compiled from an analysis of 100 unselected case histories. The onset of the preicteric stage is variable but may be abrupt, with fever, chills, generalized myalgia and symptoms common to an infectious systemic disease.

Sixty-one per cent of our patients fall into this group having a moderately abrupt onset of the disease. The temperatures ranged from 99 to 104.6 F for from one to seven days. The average duration of fever was three days, and 92 per cent of the patients were febrile for one to three days only. The temperature was usually relatively low and irregular and fell by lysis. In addition to this type of temperature curve, 3 patients had a low grade fever, with temperatures of 99 to 100 F, which recurred irregularly throughout the disease. In a few instances it would recur in a typically Pel-Ebstein type of curve, with an afebrile period of a week or ten days followed by a short interval of fever for one to three days. No other cause for the fever except the hepatitis could be ascertained in these patients. The vast majority did not exhibit this phenomenon, but in a small percentage it was a noteworthy feature.

In the remaining 39 per cent the onset was more insidious and was manifested by anorexia, nausea, vomiting, weakness, vague gastrointestinal symptoms or a dull aching in the right upper quadrant or both upper quadrants of the abdomen. No fever or chills were noted by this group. There was a slight tendency toward bradycardia during this stage, but this was rarely a striking feature.

During the preicteric stage 34 per cent of the patients had chilly sensations and an additional 29 per cent had definite rigors. Simultaneously with the chills and fever, 32 per cent had symptoms of a mild coryza, with nasal discharge or a nonproductive cough. Some stated they felt as if they had influenza, and 2 per cent had an associated sore throat. Early in the course of the

disease, prior to the development of a definite jaundice, it was almost impossible to distinguish this stage from an early atypical pneumonia, influenza, nasopharyngitis or malaria.

Anorexia was the most important early differential diagnostic guide during this period. Although a frequent symptom of the other diseases mentioned, it was not usually so severe and well defined as it was in patients with epidemic hepatitis. Almost from the onset, usually during the first few days, anorexia became the outstanding single symptom and was present in 87 per cent of the patients. This was frequently associated with nausea, which was an important early symptom in 84 per cent of the patients. Not infrequently even the sight or smell of food was sufficient to produce this complaint.

Although anorexia and nausea were frequent, vomiting was noted in only 51 per cent, and this was never severe at this stage or subsequently in the majority of the patients studied.

Pruritus was unusual during the preicteric phase but was subsequently noted in varying degrees of severity by 39 per cent of the patients. In only 2 patients was the pruritus severe or troublesome.

Diarrhea, usually mild, with three to four loose, watery stools without blood, pus or mucus, occurred in 33 per cent during the preicteric or early icteric phase of the disease. This contrasts with the 22 per cent in whom a tendency toward constipation developed. Diarrhea was also encountered frequently in the late icteric stage, during the transition from a low fat diet to a regular diet. At this time a few loose stools were frequently noted.

Other symptoms developed during this period. One was a sense of fullness in the epigastrium or right and left upper quadrants of the abdomen. An ache high in the back opposite the liver and spleen associated with a dull ache in the hepatic area anteriorly is common. This was usually described as a "dull hurting" which was frequently worse at night or with riding over rough roads in an army vehicle. At times, with jarring it became severe and sharp and was referred to the right shoulder.

"Heart burn," transitory dizziness, weakness, easy fatigability, headache (usually frontal or behind the eyes) and pains in the joints without objective redness, swelling or increased heat were frequently encountered in the early stage. The average duration of the preicteric stage was four and seven-tenths days. The frequency of the various symptoms in epidemic hepatitis is shown in table 1.

During the latter part of the preicteric stage the disease pursued one of two courses. Either it

<sup>5</sup> Epidemic Hepatitis or Catarrhal Jaundice, editorial, J A M A 123 636 (Nov 6) 1943

remained so mild that jaundice never developed, or the patient rapidly became deeply or moderately icteric

*Icteric Stage*—The transition from the pre-icteric stage to that of a definite icterus was characterized by the appearance of dark amber urine and jaundice. The jaundice usually followed the febrile period but occasionally developed simultaneously with the fever. The average time for jaundice to appear was four and seven-tenths days after the onset of fever but varied from one day to as long as several weeks. The duration of the icterus was variable, ranging from sixteen days to seven or more months. The average time for the icterus index to remain abnormally high (over 12) was thirty-nine and two-tenths days.

The maximum degree of icterus was usually reached during the first two to three weeks, then

TABLE 1—Incidence of the Predominant Symptoms in One Hundred Patients with Epidemic Hepatitis

Symptom	Incidence (Percentage)
Anorexia	87
Nausea	84
Chills and chilly sensations	63
	{ Chills 29
	{ Chilly 34
Fever	61
Vomiting	51
Pruritus	39
Myalgia	34
Diarrhea	33
Coryza (at onset)	30
Constipation	22
Sore throat (at onset)	2

it precipitously fell to a low elevated level, maintained a plateau at the slightly elevated level for several weeks and then gradually returned to normal. The rapidity of the fall in the icterus index and the concurrent relief of symptoms which accompanied it were frequently dramatic. This is illustrated in table 4. A rapid rise and fall of the icterus index was the rule in the majority of the patients. The rapid subsidence of jaundice, however, was one of the most misleading features of this disease, as the underlying hepatitis remained active and there was evidence of functional hepatic impairment both clinically and by the hippuric acid test long after the jaundice had subsided. These data are summarized later in this paper.

There was no definite correlation between the degree of icterus and the severity of the hepatitis. Not infrequently some of the patients with an icterus index never higher than 18 throughout the course of the disease appeared sicker, and the

course was more chronic than that of some who became deeply jaundiced and had an icterus index of over 100.

During this icteric stage, the patients' symptoms tended to subside rapidly but there might be frequent exacerbations with recurring enlargement and tenderness of the liver and occasionally a second or third rise in the icterus index. This tendency to relapse after the disease has apparently subsided is under certain conditions a characteristic feature of this type of hepatitis.

*Convalescent Stage*—After the jaundice had initially subsided to a low elevated level, the period of convalescence began. This is an extremely important period in the treatment of this disease, and this stage was characterized by a tendency toward frequent relapses. The exact frequency of relapses in this series is unknown because of our inability to obtain adequate follow-up studies on the majority of the patients after they had been discharged from the hospital. Relapses while the patients were still in the hospital under observation were frequent enough for us to observe two precipitating factors.

Relapses were frequently observed in patients in whom an intercurrent infection of the respiratory tract developed. The severity of the relapse seemed to depend on the severity of the infection of the respiratory tract. In general this type of relapse was relatively mild, although associated with an exacerbation of the patient's symptoms, transitory hepatic enlargement and a rise in the icterus index. Frequently it was so transitory that the usual course of the disease was not greatly prolonged.

The second, and more severe, type of relapse was that which resulted from too much physical exertion prior to the time the hepatitis was completely cured. The amount of exertion necessary to produce this was variable, depending on the degree of healing of the hepatitis and the type of exertion. We have repeatedly seen an exacerbation follow the climbing of two flights of stairs or a short leisurely walk. Running, jumping and not infrequently simply riding in an army vehicle have been precipitating factors. The rigors of military life and the fatigue of actual combat conditions has been a definite factor in precipitating a relapse after the patient was considered well.

A recurrence resulting from fatigue was characterized by a dull ache in the region of the liver with an occasional sharp cutting pain which might be referred to the back or to the right shoulder. At times the pain in the region of the liver was severe and closely simulated that of acute chole-

cystitis. Rarely pain was experienced in both upper quadrants of the abdomen. Associated with this pain was a return of anorexia, nausea and vomiting, usually with an increase in the icterus index and bilirubin. The liver usually enlarged and became palpable and tender. In an occasional patient the liver did not become palpable, but a transitory hepatomegaly was the rule during a relapse. There seemed to be some correlation between the degree of fatigue and the severity of the relapse. In general, the more fatigue experienced the more severe and prolonged the recurrence.

Those relapses which occurred in patients after a return to actual combat duty tended to be more severe than those developing in patients while they were in the hospital, and not infrequently they were more severe than the original attack. These patients required a prolonged recovery period, and in a small percentage a chronic hepatitis developed.

In an attempt to determine why these patients, who were seemingly well, tended to have an exacerbation on returning to even mild activity, various studies were made. In these studies it was found that the sedimentation rate was frequently markedly elevated for several weeks after the icterus index had returned to normal and that hepatic function, as measured by the synthesis of hippuric acid, was seriously impaired for as long as two months after the icterus index had returned to normal. The activity of the hepatitis and the functional inefficiency of the liver over such a period would seem to favor the development of relapses.

The rapid fall in the icterus index and the apparent rapid clinical improvement in these patients after treatment is started are treacherous, misleading and characteristic features of this type of hepatitis. Residual hepatic damage and activity of the hepatitis may persist for weeks or months after the icterus index has returned to normal. We feel that this residual activity and functional hepatic insufficiency are the basis for the tendency to relapse when the hepatitis has seemingly subsided.

It is important to realize that the hepatitis is not cured in the majority of patients when the icterus index returns to normal and the patient begins to feel well. If cautious, conservative treatment with the emphasis on rest in bed and adequate intake of fluids is insisted on for one or two weeks after the icterus index has returned to a normal level, we believe that most relapses can be avoided or minimized. If this is not done, relapses occur frequently and a chronic hepatitis may develop.

*Physical Examination*—The incidence of physical findings in 200 patients with infectious hepatitis with jaundice is shown in table 2.

The degree of icterus varied from a faint tint of the scleras to an orange-bronze discoloration of the scleras and skin. A few of the patients were so deeply jaundiced that they had a dusky, cyanotic hue added to the deep yellow color of the skin.

Hepatic enlargement is a characteristic feature of this disease, and the liver was clinically palpable in 58 per cent of the patients. The degree of enlargement was at times striking and has been observed a full handbreadth below the costal margin. An enlargement of 1 or 2 fingerbreadths below the right costal margin was the rule. Hepatic tenderness was also a common finding, being present in some degree in 66.5 per cent of

TABLE 2—Physical Findings in Two Hundred Patients with Epidemic Hepatitis with Jaundice

Finding	Incidence (Percentage)
Icterus of skin	100
Icterus of scleras	100
Lymphadenopathy <sup>6</sup>	81
Axillary	70
Inguinal	54.5
Axillary and inguinal	33
Cervical	19
Generalized	15.5
Epitrochlear	6
Hepatic tenderness	66.5
Hepatic enlargement (palpable) <sup>7</sup>	58
Conjunctival injection	27
Mild	10
Moderate	15
Intense	2
Enlargement of spleen (palpable)	9
Injection of palate	5.5
Conjunctival hemorrhage	2
Dermatitis	2

the patients. The degree of tenderness varied from a mild sense of soreness to severe pain on deep palpation. In 33.5 per cent no tenderness was noted at any time throughout the course of the disease.

Lymphadenopathy, present in some degree in 81 per cent of the patients, was frequently a striking feature. The lymph nodes ranged in

<sup>6</sup> In evaluating the lymphadenopathy we carefully excluded all patients having abrasions, dermatitis, furuncles or other lesions that might have produced a similar enlargement of the nodes from a purely local cause. It is therefore felt that the lymphadenopathy is a characteristic feature of this disease.

<sup>7</sup> A roentgenogram of the liver and spleen to determine the size of these organs was made in 31 cases, and both liver and spleen were found enlarged in 26 of the 31 cases. In 5 cases of hepatitis without icterus the roentgenogram has revealed both hepatic and splenic enlargement to be present.

size from that of a small pea to that of an English walnut. The size and consistency of the enlarged nodes varied with the different stages. During the early part of the disease, the nodes were frequently soft, mushy, freely movable, nontender and discrete, later they became firm, smaller and shothke. There was no tendency toward suppuration or matting together. The axillary and inguinal nodes were most frequently involved. The frequency and location of the lymphadenopathy are listed in table 2.

The spleen was clinically palpable in 9 per cent of the patients. The splenomegaly was frequently transitory in the early stages or was found later in the more severely ill patients. In an attempt to evaluate this further, roentgenograms were made of the liver and spleen to determine the size of these organs in 31 patients at varying stages of the disease. The liver and spleen were found enlarged in 26 of the 31 patients thus studied. From this evidence it would seem that both hepatic and splenic enlargement are frequently encountered and are characteristic features of epidemic hepatitis.

Conjunctival injection, present in 27 per cent of the patients, is of interest in view of its reputed importance in the diagnosis of Weil's disease. The degree of injection was considered to be mild in 10 per cent, moderately severe in 15 per cent and severe in 2 per cent of the patients. The cause of the injection of the conjunctivas is unknown, but it is doubtful that it has any diagnostic significance. There was some tendency for the degree of injection to coincide with the degree of icterus. Those patients having the highest and most persistent icterus index tended to have the more severe conjunctival injection. Conjunctival hemorrhages were noted in 2 per cent of the patients, these were small areas 1 to 3 mm in diameter, located on the outer medial part of the bulbar conjunctiva. In none of these patients exhibiting conjunctival injection or hemorrhage was it possible to demonstrate any type of leptospiras in dark field examinations of either the blood or the urine.

Injection of the soft palate was noted in 5.5 per cent of the patients early in the preicteric stage of the disease, and, since a majority of the patients were admitted to the hospital after the development of jaundice, this may be a more frequent early observation.

A dermatitis of any type was rare, as only 5 of the 448 patients had any type of cutaneous rash at any time during the course of the hepatitis. In 3 of these there was a diffuse, macular erythematous rash over the abdomen, the anterior part of the chest and the upper extremities. This

type of dermatitis was seen early in the disease shortly after or coincidental with the febrile period of the preicteric stage. The rash completely disappeared within three days in all cases.

In 1 patient a generalized urticaria developed, and another had a few petechiae during the icteric phase of the hepatitis. In none was the rash severe or troublesome.

#### LABORATORY STUDIES

**Blood**—In an attempt to evaluate the effect of this illness on the blood, we studied a group of 100 patients by means of weekly blood counts throughout the course of the disease. A summary of these data is shown in table 3, which gives the average range of the white blood cell and differential counts at weekly intervals.

The average range of the white blood cell count was 7,149 to 9,975, but the actual range varied from a leukopenia of 2,700 to a leukocytosis of 38,600. It was unusual for the white

TABLE 3—Average Weekly White Blood Cell Count and Differential Count of One Hundred Patients with Epidemic Hepatitis

Week	Initial	1st	2nd	3rd	4th	5th	6th
Polymorphonuclear							
Leukocytes	49.5	50.6	52.0	51.3	49.8	51.3	49.2
Lymphocytes	44.1	42.5	41.0	40.3	41.6	39.3	40.0
Mononuclear							
Leukocytes	3.2	3.7	3.0	3.9	3.7	5.0	6.5
Eosinophils	2.0	2.3	3.0	3.5	4.4	3.3	3.0
Basophils	1.2	0.9	1.0	1.0	0.5	1.1	1.3
White blood cell count	7,149	7,751	7,913	7,727	9,268	7,894	9,975

cell count to be over 12,000, and only 3 per cent of the patients in this group had a leukocyte count of over 12,000. The highest white blood cell count was noted in the patient who died and was probably a reflection of the severe complications which were observed in this patient. A leukopenia or a normal white blood cell count is considered to be more characteristic of the disease. The leukopenia is especially characteristic during the febrile or preicteric stage and shortly thereafter. There was a slight tendency in many of the patients for the white blood cell count to rise slowly to a high normal value or slight leukocytosis as the disease progressed throughout its course.

The differential white blood cell count usually showed a relative lymphocytosis throughout the disease, the percentage of lymphocytes being as high as 87 per cent of the white blood cells. In an occasional patient no increase in the relative number of lymphocytes was observed, but this was unusual.

There is little if any tendency toward the development of anemia in the average patient.

without complications. In only 3 per cent of the 100 patients studied by repeated examination of the red blood cell counts, hemoglobin content and hematocrit values was any significant anemia noted. In 2 of these patients a mild, transitory anemia developed, which was unexplained and required no treatment. The third patient had repeated severe hemorrhages from a gastritis with large gastric ulcerations and subsequently died. Hemorrhage from gastrointestinal ulcerations, especially if accompanied with a prolonged prothombin time and coagulation time, may result in death. Hence it is felt that, although the tendency toward the development of anemia is relatively slight, one should be constantly on the alert for the development of an acute anemia secondary to hemorrhage from the gastrointestinal tract. This is the only significant type of anemia seen in this series and occurred only in the patient with a rapidly fatal course.

TABLE 4—*Van den Bergh Reactions and Icterus Indexes of One Hundred Patients with Epidemic Hepatitis (by Week)*

Week of Disease	Direct (Percentage)	Biphasic (Percentage)	Indirect (Percentage)	Average Icterus Index (Units)
Initial	37	63	0	49.4
Second	33	66	1	28.1
Third	14	86	0	19.6
Fourth	2	95	3	16.6
Fifth	0	94	6	14.3
Sixth	0	100	0	14.1
Seventh	0	88	12	14.2

#### *Icterus Index and van den Bergh Reaction*—

One hundred patients were studied by weekly determinations of the icterus index and qualitative van den Bergh reaction. All icterus index determinations were made by the Bernheim method,<sup>8</sup> and the Gibson and Goodrich<sup>9</sup> modification of the van den Bergh method was used in this study. Table 4 illustrates these data.

The initial icterus index was made the day following the patient's admission to the hospital, which averaged eight and one-half days after the onset of symptoms and three and seven-tenths days after the development of jaundice. The table illustrates the characteristic rapid rise and fall of the degree of icterus, followed by a prolonged recovery period of two to six weeks before again returning to normal. The icterus index was usually not markedly elevated but ranged from a low of 16 to the amazing high of 563. A comparison of the van den Bergh reactions reveals that throughout the course of the disease the

biphasic reaction was typical, but during the first two weeks a direct van den Bergh reaction was observed in over one third of the patients. In contrast to the frequency of direct reactions during the first two weeks, an indirect reaction was obtained almost entirely during the period of convalescence.

#### *Dark Field Examination for Leptospiras*—

Because of the fact that the majority of these patients were exposed to conditions which favored the transmission of Weil's disease and had frequently had to remain for days in wet fox holes, it became necessary to rule out *Leptospira icterohaemorrhagiae*, *Leptospira canicola* and other spirochetes as the etiologic agents involved.

Eighty-four dark field examinations of the blood for these organisms were made during the first ten days of the illness in 76 patients. Forty-four dark field examinations of the urine were made for 44 patients after the tenth day of the disease. In none of these examinations were leptospiras, spirochetes or spirilla demonstrated. Blood was also cultured repeatedly in Noguchi's medium and incubated at room temperature and at 37 C under aerobic and anaerobic conditions. No evidence of growth was observed after sixteen days of incubation. Intraperitoneal inoculation of blood from 2 patients into a guinea pig also gave negative results.

Artefact spirochete-like bodies similar to those reported by Schultz<sup>10</sup> were frequently observed in over 50 per cent of the dark field examinations of the blood. These were considered to be artefacts, because they exhibited no active motion, were rigid and did not form spirals and could not be grown on any available medium or by inoculation in guinea pigs. They could not be stained with polychrome methylene blue or nigrosin or by silver impregnation methods. These artefacts, which were 8 to 10 microns in length and 0.5 micron in width, are mentioned only to emphasize the difficulties encountered and a possible source of error in dark field examinations of the blood. Kuzzell,<sup>11</sup> studying the same epidemic, has reported somewhat similar observations.

*Heterophile Agglutination Test*—Because of certain similarities of this disease to infectious mononucleosis, a heterophile agglutination test was performed on 18 patients having the highest lymphocyte count and most pronounced lymphadenopathy. All results were negative.

<sup>10</sup> Schultz, E. W. The Pseudo Spirochaetes Derived from Red Blood Cells, *J. Lab. & Clin. Med.* 8: 375 (March) 1923.

<sup>11</sup> Kuzzell, W. M. Artifact Spirochaetes in Infectious Hepatitis, *M. Bull. North African Theat. Op.* 1: 24 (Feb.) 1944.

<sup>8</sup> Methods for Laboratory Technicians,<sup>4</sup> p. 119.

<sup>9</sup> Methods for Laboratory Technicians,<sup>4</sup> p. 120.

**Fragility Test**—In an attempt to evaluate any hemolytic factor that might be present in this disease, we studied 66 patients by determining the fragility of the red blood cells according to the method of Sanford<sup>12</sup> None of these tests revealed any increased hemolysis as compared with that of the control In fact, a majority of the tests revealed an increased resistance of the red blood cells to the hypotonic saline solution

**Sedimentation Rate**—One hundred and fifty-seven patients were studied by means of determination of the sedimentation rate according to the method of Wintrobe and Landsberg<sup>3</sup> with correction for anemia These tests were performed at varying intervals throughout the course of the disease In this group the sedimentation rate was almost invariably elevated after the first week of the disease and frequently remained persistently elevated throughout the course of the illness Not infrequently it remained sharply elevated (25 to 30 mm) for several weeks after the icterus index had returned to normal, slowly returning to a normal level as the hepatitis subsided or healed The persistently elevated sedimentation rate after the icterus index had returned to normal was also compared with the clinical evidence of an active hepatitis and with evidence of hepatic dysfunction as determined by the synthesis of hippuric acid These studies indicate that in many of these patients there was some residual activity of the hepatitis and considerable functional impairment of the liver long after the icterus index had returned to normal In an occasional patient with mild disease there was no increase in the sedimentation rate

**Hippuric Acid Test**—One hundred and forty-three hippuric acid tests of hepatic function were performed on 88 unselected patients with infectious hepatitis at varying stages of the disease An analysis of these results reveals that there is frequently considerable impairment of hepatic function, as determined by this test In 21 cases the excretion of hippuric acid was repeatedly determined throughout the course of the disease and for several weeks or months after the icterus had subsided These data are summarized in table 5

Only 5 of the 21 patients studied by the hippuric acid test were able, after the administration of sodium benzoate, to excrete 3 Gm or more of benzoic acid in the form of hippuric acid during the period of observation, while the remaining 15 patients were never able adequately to conjugate

TABLE 5—Serial Studies Comparing the Results of the Hippuric Acid Test of Liver Function with the Icterus Index, the Sedimentation Rate and the White Blood Cell Count in Twenty-One Patients with Epidemic Hepatitis

Case	Day of Illness	Icterus Index at Time of Test	Hippuric Acid, Gm	Day Icterus Index Returned to Normal	Highest Icterus Index	Corrected Sedimentation Rate (Wintrobe)	White Blood Cells
1	16	36		33	48	28	4,200
	25	17				16	7,600
	35	10	2.72			18	6,750
	49	10	2.92			12	6,200
	61		4.01				
2	50	10		41	51	21	7,800
	60	13				20	8,200
	75	10	2.12			13	6,900
	87	10	1.66				
	97	8	2.26				
3	52		2.28	64	27	10	9,200
	65	12	2.96			3	7,400
4	132	9	2.04	132	250	40	
	152	8	2.76			16	9,900
	159	1	2.53				
5	110	39	1.16	135	126	36	8,900
	135	10	1.92			14	7,900
6	21	48		78	78		
	61	13	2.04			34	6,850
	71	15	1.88			37	
	83	9	2.83			21	5,800
7	18	27		34	27		7,050
	38	12	2.15			16	3,250
	68	13	1.84			5	1,350
	82	10	2.72				5,300
8	11	39	3.32	19	39		
	28	7	3.12				13,700
9	67	6	1.40	31	39	20	6,750
	80	8	1.80			32	7,000
	85	8	3.04				
10	53	14	2.72	10	150	14	5,700
	68	7	2.98			7	
11	36	10		33	32	0	6,150
	56	11	1.96			15	6,650
	68	10	2.64			4	
	75	10	2.36				
	85	8	2.84				
12	51	8	1.88	31	23	0	7,800
	73	10	2.44				
13	83	9	2.80				
	150	35	0.95	198	108	30	9,400
	177	26	1.84			30	15,700
	198	12	2.44			13	11,500
	215	10	2.48			16	10,600
14	42	11	2.56	42	46	12	10,700
	55	10	2.60			14	6,450
15	59	10	2.92				
16	65	6	1.48	47	42		8,400
	77	9	2.40	42	84	23	
17	87	8	2.84				
	40	114	0.00	Never normal	173	21	
18	55	126	0.00			21	4,500
	70	126	1.28			32	6,650
	31	22	1.52	60	111	54	9,950
19	56	13	1.60			30	7,800
	69	8	1.68			21	
	78	6	2.04			8	7,300
	85		3.13				
20	51	10	2.34	30	64	15	6,900
	63	8	0.86				
	76	10	1.48				
	87	6	2.37				
21	39	12	1.69	39	84	20	5,050
	51	12	1.52			6	
	59	10	2.04			6	
	71		1.66				
21	14	9	1.24	14	19	10	5,500
	27	9	1.96			11	
	42	11	3.46				

12 Todd, J. C., and Sanford, A. N. Clinical Diagnosis by Laboratory Methods, ed 10, Philadelphia, W. B. Saunders Company, 1943, p. 327

the benzoic acid and amino acetic acid during this period. The average period required for these patients to approach a normal excretion of hippuric acid was thirty-eight days after the icterus index had returned to a normal level of 10 to 12. The actual range of time required for the functional capacity of the liver to return to a near normal after the jaundice had subsided was from one to sixty-four days and in some cases might be much longer. The exact time required for the liver to regain its normal functional efficiency is unknown, as it was not possible to follow these patients for a longer period. This evidence indicates that at least some functional impairment of the liver exists long after the icterus has subsided and the patient has seemingly recovered and is of importance in explaining why these patients so frequently had relapses after the hepatitis was apparently cured.

Unfortunately, facilities were not available at the time of this study to permit other tests of hepatic function to be performed.

*Urine*—In this series of 448 patients a transitory albuminuria was noted in only 18. This always occurred during the first two weeks of the disease and was seen only in the initial urinalysis following admission in 16 of the 18 patients. In these 16 patients the albuminuria did not persist over two days. One patient had a mild albuminuria (1 to 2 plus) for seven days, and the patient who died had a persistent albuminuria until his death on the sixth day after his admission. With this exception, the albuminuria was never severe and disappeared with rest in bed and adequate fluids.

No red blood cells, white blood cells or casts were found in the urine of any of these patients, and their ability to concentrate urine was unaffected.

In contrast to the experience reported by Turner and others<sup>13</sup> with postvaccinal hepatitis, a high or normal specific gravity of the urine was noted in all of our patients having a transitory albuminuria. Determinations of the non-protein nitrogen content of the blood were made on all patients having albuminuria, and in only the patient who died was this found elevated.

*Stools*—The stools were carefully observed for color and bile at weekly intervals for 101 patients and less frequently for the remainder of the group. Acholic, clay-colored stools were rarely

encountered, although some diminution of bile pigment was common in the stools of the majority of the patients at some time during the course of the disease.

*Serologic Reactions*—The Kahn reaction of the blood was determined on 146 patients on their admission to the hospital and was negative in all except 3. The reactions of these 3 patients remained positive during only the first three weeks of the disease and subsequently became negative after the icterus subsided. These were considered false positive reactions, because there was no history or evidence of syphilitic infection in any of these patients.

*Coagulation Time*—A small group of patients were studied by means of the test for coagulation time during the first five weeks of the disease. The capillary tube method<sup>4</sup> was used. Fifty-two tests were made at the time of the patients' admission. None of these tests revealed an abnormal coagulation time, the average coagulation time being five and nine-tenths minutes. Forty-two tests were made one week later, five of which showed a prolonged coagulation time of over eight minutes, the average time being six and one-tenth minutes. Twenty-seven tests were done during the third week, with five showing a prolonged coagulation time and with an average time of six and two-tenths minutes. During the fourth week eight tests were made, and three of these revealed evidence of a prolonged coagulation time, the average time being six and two-tenths minutes. Although the number of tests performed is small, there seemed to be an increasing tendency toward the development of a prolonged coagulation time in a small percentage of the patients studied.

Prothrombin times were not determined, as facilities for this determination were not available at the time of this study.

The relative infrequency of a hemorrhagic tendency as noted clinically was remarkable in this series. Only an occasional patient had a mild epistaxis, and in only 2 was the bleeding sufficiently prolonged to warrant the administration of vitamin K. In these 2 administration of vitamin K seemed to be effective in controlling the hemorrhage when other remedies had failed, but administration of vitamin K was ineffective in the fatal case.

The case history of the 1 fatality in the icteric group follows.

#### REPORT OF A CASE

A 26 year old white officer was admitted to the hospital on Dec 23, 1943, with a chief complaint of jaundice.

<sup>13</sup> Turner, R. H., Snively, J. R., Grossman, E. B., Buchanan, R. N., and Foster, S. D. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Especial Consideration of Severe Attacks, *Ann Int Med* 20. 193 (Feb) 1944.

The patient was in good health until about seven days prior to his admission, when, on December 16, he began having chills and fever associated with severe headache, backache and anorexia. He was nauseated frequently but did not vomit. These symptoms persisted, and very little fluid or food was taken. Weakness became noticeable. Four days before his admission he noted that his urine was a dark yellow, and the next day jaundice of the skin and scleras was observed for the first time. On December 21 he was admitted to an evacuation hospital, where he remained for two days. His temperature while he was there varied from 102 to 103 F. The jaundice became progressively deeper, the nausea persisted, and little or no fluid was taken. Malaise, anorexia and nausea continued, and the weakness became more pronounced.

For two months prior to the onset of this illness the patient had a diarrhea consisting of six to eight watery stools a day without pus, blood or mucus. As he felt well in all other respects, this was considered a nuisance only, and medical aid was not sought. At the onset of the illness which brought him to the hospital the diarrhea ceased. There was no previous history of jaundice or of disease of the gallbladder.

Physical examination showed a well developed and fairly well nourished man, who was extremely jaundiced and who appeared to be acutely ill. There was evidence of extreme weakness in every effort made by the patient. There were a few petechiae scattered over the abdomen and the lower part of the back. There was evidence of moderate dehydration. The cervical and axillary lymph nodes were moderately enlarged, soft and nontender. The heart was normal in size, but the sounds were of poor quality. The lungs were clear. The abdomen was soft and flat, with slight tenderness in the right upper quadrant. The liver, spleen and gallbladder were not palpable. The liver seemed small on percussion.

The blood pressure was 100 systolic and 70 diastolic. The temperature was 99 F, the pulse rate 80 and the respiratory rate 20.

Examination of the blood showed a red cell count of 3,140,000, with a hemoglobin content of 75 per cent (Tallqvist). The white blood cell count was 10,250, with 73 per cent neutrophils, 26 per cent lymphocytes and 1 per cent basophils. The urine, which was not obtained until after fluids were given, was a dark amber color with a specific gravity of 1.009. There was no albumin or formed elements, but the test for bile elicited a positive reaction. Culture of the blood, including culture for leptospiras and spirochetes on Noguchi's medium, showed no growth. A guinea pig was inoculated with the patient's blood, and two dark field examinations of the patient's serum for leptospiras were made. Results of all of these procedures were negative. The icterus index on the patient's admission was 405, and the van den Bergh reaction was direct. The quantitative van den Bergh test showed 1.74 mg of bilirubin. Culture of the stools and examination revealed no ova or parasites. The bleeding time was five minutes. A fragility test showed beginning hemolysis in 0.34 per cent sodium chloride solution and complete hemolysis in 0.28 per cent. This result was normal as compared with the control.

A roentgenogram of the chest, made with a portable apparatus four days after his admission, showed passive congestion in the pulmonary fields. The cardiac outline appeared slightly enlarged. The patient was given a high carbohydrate liquid diet, which he tolerated well. This was supplemented daily by 1,000 cc of an intravenously injected 5 per cent dextrose solution, keeping his daily fluid intake above 3,000 cc. After hydration was accomplished, a repeated examination of the blood

two days after his admission revealed a red cell count of 1,950,000 and a white cell count of 38,600, with 82 per cent neutrophils and 18 per cent lymphocytes. Daily transfusions of 500 cc of whole blood were given. During the first three days the patient seemed slightly improved, in spite of the fact that the watery diarrhea had returned. There was still extreme weakness, with headache and backache but with less nausea and vomiting. The icterus of the skin and scleras became deeper, and on December 28 the icterus index was 526. The liver became palpable at the right costal margin. The diet was supplemented daily by 6 multivitamin capsules,<sup>14</sup> 50 mg of thiamine hydrochloride injected intravenously and 35 mg of menadione in oil (vitamin K) injected subcutaneously.

On the fourth day in the hospital he began having some abdominal distention, which gradually became more pronounced. There was also generalized abdominal tenderness, but no ascites was detected. The edge of the liver was palpable 1 fingerbreadth below the costal margin and was tender. The temperature, which had ranged from 99 to 100 F since his admission, rose to 101.8 F. The patient's condition became progressively worse. He was nauseated and retched often but did not vomit. A Levine tube was inserted into the stomach, and 1,000 cc of dark bloody fluid was removed. The distention was controlled somewhat, but after voiding on December 28 he did not void again for thirty hours. This last specimen was of a dark green color, gave a 2 plus reaction for albumin and was strongly positive for bile. Neither tyrosine nor leucine crystals were found. An icteric frost was observed on the forehead and cheeks. The nonprotein nitrogen content was 198 mg per hundred cubic centimeters and the icterus index 563. In spite of his steadily declining condition, the patient remained conscious. Dulness was noted at the bases of the lungs, and a few rhonchi were heard. The anemia persisted in spite of daily transfusions of whole blood. A final examination of the blood on December 29 revealed a red cell count of 2,250,000 and a white cell count of 34,300, with 95 per cent neutrophils and 4 per cent lymphocytes.

The patient died on the sixth day in the hospital and the thirteenth day of his illness.

#### PATHOLOGIC DATA

The body was that of a well developed but poorly nourished, 26 year old white man that came to autopsy two hours post mortem.<sup>15</sup> The skin was intensely icteric. The main pathologic changes were confined to the kidneys, the stomach and the liver.

The left kidney weighed 310 Gm, and the right kidney weighed 280 Gm. The kidneys were dark green. The cortex measured 0.8 cm in width. The most remarkable feature was the abnormal color. The cortical and medullary portions were deep red, in contrast to the prominent red striations. The stomach contained approximately 200 cc of unclotted blood. The mucosa of the stomach was extremely hemorrhagic. The remainder of the gastrointestinal tract was essentially normal, except for congestion. The liver weighed 2,100 Gm. The enlargement was confined primarily to the right lobe. The liver was deep reddish brown in

14 According to the label of the package each capsule contained 2,500 USP units of vitamin A, 200 USP units of vitamin D, 10 mg of thiamin hydrochloride, 1.5 mg of riboflavin, 37.5 mg of ascorbic acid and 100 mg of nicotinamide.

15 Major David K. Gotwald, Medical Corps, Army of the United States, Chief of the laboratory service, performed the autopsy and furnished the autopsy report.

color and of a normal consistency. On section the liver appeared free of macroscopic areas of necrosis and hemorrhage. No intrahepatic or extrahepatic biliary obstruction was present. Except for a moderate enlargement of the spleen, the lymphoid elements were not remarkable.

*Microscopic Studies*—The kidneys revealed an intense bile nephrosis. There were swelling and necrosis of the convoluted tubular cells. Great numbers of dense pigmented casts were present in the lower segments of the nephrons. These casts gave a staining reaction for bilirubin. The stomach showed the presence of a severe hemorrhagic gastritis. There were a moderately severe periportal inflammatory infiltration and a few minute areas of necrosis in the liver. There was no central necrosis of the lobules.

Death in this case was considered to be due to uremia resulting from the bile nephrosis occurring in the preatrophic stage of epidemic hepatitis. Weil's disease was ruled out by the absence of spirochetes in the blood and the urine on dark field examination, on guinea pig inoculation, on culture and in tissues stained for spirochetes. Yellow fever was believed to be ruled out on morphologic grounds and on the absence of exposure.

#### HEPATITIS WITHOUT JAUNDICE

Seventeen patients with hepatitis without jaundice were observed, and undoubtedly the diagnosis was frequently missed during the early part of this study. The following are the criteria we believe to be the most useful in establishing the diagnosis.

The history is of paramount importance and is no different from that of the usual patient with jaundice, except that fever may be negligible or the temperature may be so low that it is unnoticed and clinical jaundice never develops.

Anorexia is an early and constant symptom, with or without nausea or vomiting.

Vague gastrointestinal symptoms, gaseous eructation, ill defined abdominal discomfort or actual pain in the upper part of the abdomen or in the back behind the liver are the rule.

Easy fatigability and lassitude are common complaints. The history is frequently so vague that it is suggestive of a mild anxiety state with gastric fixation of the neurosis, and this possibility must be carefully evaluated.

On physical examination the scleras may be clear or have a faint, muddy, subicteric tint with some conjunctival injection. This tint is usually so slight that it may be easily overlooked.

The liver is usually enlarged and tender, or tenderness only is noted. The spleen is frequently enlarged.

Lymphadenopathy, especially soft enlarged axillary nodes, is a helpful finding in most of these cases. Generalized lymphadenopathy has been noted in a few cases.

Laboratory studies reveal a normal icterus index and van den Bergh reaction. Occasionally

an indirect van den Bergh reaction is noted. The white blood cell count is either normal or moderately elevated, to around 12,000. A relative lymphocytosis is the rule.

Urinalysis reveals an increase in urobilinogen or a trace of bile early in the disease, but these usually disappear quickly with rest in bed and adequate fluids.

In addition to these laboratory aids, we have found that a roentgenogram of the liver and spleen may aid in determining the presence of hepatic or splenic enlargement that could not be palpated on physical examination.

Hippuric acid tests were made on 7 of the patients with hepatitis without icterus. These frequently indicated extensive functional impairment of the liver (1 to 1.5 Gm excretion) but usually only a moderate or slight functional inefficiency was noted. For an occasional patient the excretion of hippuric acid was entirely normal.

It is our feeling that a combination of the characteristic history and the characteristic physical features, when associated with these laboratory changes, is sufficient to provide the diagnosis of this syndrome.

The diagnosis is not difficult during an epidemic, when one sees all variations of the same disease from the very mild to the most severe. It should not be difficult to make the diagnosis if one is aware of the fact that such an entity does exist. The clinical course is usually mild, and all symptoms tend to subside rapidly with rest in bed. The average duration of the illness in this group was three weeks, but it may be prolonged by inadequate rest or by excessive physical exertion prior to complete healing of the hepatitis.

The following case histories are presented to illustrate the characteristic findings in this syndrome.

#### REPORT OF CASES

CASE 1—A 22 year old white man was admitted to the hospital on May 8, 1944 with the following history.

He felt well until ten days prior to his admission, when he first noted a temperature of 99.6 F and frequent chilly sensations. The chilly sensations and low grade fever persisted for three days. Simultaneously pronounced anorexia, nausea and occasional vomiting developed, and his urine became darker, but it was clearing at the time of admission. During this period he was seen frequently by his medical officer, and two blood smears were negative for malaria parasites. No jaundice was noted. He continued to perform his duties, but extreme weakness and fatigability necessitated his admission to the hospital.

There was no history of malaria or any past history of a similar illness. Review by systems showed no abnormality.

Examination revealed a well developed and well nourished white man, who did not appear acutely ill. The physical examination revealed normal conditions except for an enlarged tender liver, which extended

3 fingerbreadths below the right costal margin. The liver was smooth and firm, without nodules, and was rather tender. There was no icterus of the scleras or skin. The spleen was not felt, and there was no lymphadenopathy. The temperature, pulse and respirations were normal.

Laboratory studies on his admission revealed an icterus index of 7. The van den Bergh reaction was negative. The red blood cell count was 4,500,000, hemoglobin content 90 per cent and white blood cell count 4,950, with 45 per cent neutrophils, 51 per cent lymphocytes, 4 per cent basophils and 1 per cent monocytes. The urine gave a negative reaction for bile but gave a positive reaction for urobilinogen in a dilution of 1 to 40. A hippuric acid test of hepatic function on the eleventh day of his illness revealed a synthesis of 280 Gm. The Kahn reaction of the blood was negative.

*Course*—During the first week of hospitalization the patient improved rapidly and had no further nausea or vomiting. Anorexia ceased after ten days, and the liver was not palpable after the first week. No icterus developed clinically, and the icterus index on May 23 was 7, with a negative van den Bergh reaction. Urobilinogen was present in the urine in a 1:10 dilution on the nineteenth day in the hospital. Roentgenograms of the gallbladder were made and disclosed a normal functioning gallbladder without stones. The course was uneventful, and the patient was returned to duty on the twenty-first day of hospitalization. He was asymptomatic at this time, and jaundice had not been noted clinically.

**CASE 2**—A 19 year old white youth was admitted to the hospital on February 1 with the following history. He felt entirely well until two weeks prior to his admission, when diarrhea developed, there were five or six loose stools daily for three days. No blood, pus or mucus was noted. The diarrhea ceased, but from the onset the patient had noted severe anorexia and occasional bouts of nausea without vomiting. The anorexia became more severe, a "full" feeling in the upper part of his abdomen developed, but he had no abdominal pain.

He continued duty but felt weak and drowsy and noted that he tired easily. During this period his urine was intermittently dark-colored, but at no time was jaundice noted. Gaseous eructations and an inability to eat fatty or greasy foods developed. He had no fever, chills or other symptoms. There was no history of malaria or of disease of the gallbladder, and a careful review by systems revealed no other symptoms.

On physical examination there were seen a faint subicteric tint to the scleras and moderate enlargement of the cervical, axillary and inguinal lymph nodes. The liver was 1 fingerbreadth below the right costal margin and was tender. The spleen was not felt. The remainder of the examination revealed nothing abnormal. There was no icterus of the skin. The temperature, pulse and respirations were normal.

Laboratory studies made on his admission showed a red blood cell count of 4,460,000, a hemoglobin content of 85 per cent and a white blood cell count of 13,150, with 36 per cent neutrophils, 56 per cent lymphocytes, 7 per cent eosinophils and 1 per cent basophils. The specific gravity of the urine was 1.025, and the urine showed no sugar or formed elements but was positive for urobilinogen in a 1 to 100 dilution. The icterus index was 6, the van den Bergh reaction was negative. Examination of a thick drop for malaria gave negative results. The Kahn reaction of the blood was negative.

One week after his admission the white blood cell count was 12,800, with neutrophils 46 per cent, lympho-

cytes 44 per cent, monocytes 4 per cent, eosinophils 4 per cent and basophils 2 per cent. The icterus index was 8, and there was a negative van den Bergh reaction.

A roentgenogram of the liver and spleen revealed both hepatic and splenic enlargement. Roentgenologic studies of the gallbladder and stomach showed both to be normal.

Repeated examinations of the stools for parasites and ova gave negative results. Two cultures of the stools showed no typhoid-dysentery organisms.

Eleven days later the icterus index was 7 and the van den Bergh reaction negative. The white blood cell count was 8,600, with 50 per cent lymphocytes. The urine showed a trace of bile, and the reaction for urobilinogen was positive in a 1 to 20 dilution. Two heterophile agglutination tests gave negative results. A hippuric acid test of hepatic function revealed a synthesis of 215 Gm in four hours. The icterus index and van den Bergh reaction remained normal. Within ten days after his admission the liver had returned to a normal size and could not be palpated.

*Course*—During the first two weeks of the patient's hospitalization anorexia was severe and then gradually decreased until he became asymptomatic four weeks after his admission. At no time did clinical jaundice develop, and he was asymptomatic when discharged, on March 13.

#### TREATMENT

The general principles of treatment in this series were primarily concerned with relieving the patients' symptoms and preventing relapses or residual hepatic impairment.

A high carbohydrate, low fat, moderate protein diet was the standard type used and was tolerated well. Multivitamin tablets<sup>14</sup> were given to all patients throughout the course of the illness as a supplement to the low fat diet.

In addition to these measures, intermediate feedings of fruit juices and hard candy were given to all the patients between meals. This supplemented the caloric intake and seemed to be of value during the early part of the illness, when the intake of food was at its lowest level.

Rest in bed, especially during the early stages of the disease, is considered to be more essential in promoting a rapid recovery and in preventing relapses than any other single factor.

If sufficient rest is obtained, relapses can be reduced to a minimum and the tendency for a chronic hepatitis to develop can be avoided in the vast majority of these cases. If a relapse develops, further rest in bed and avoidance of physical fatigue promptly relieve the patient's symptoms.

Of importance almost equal to rest in bed is an adequate intake of fluids. These can be in the form of water or fruit juices, the latter being especially efficacious and well tolerated. A fluid intake of at least 3,000 cc daily is considered essential for the prompt relief of the patient's symptoms and of the degree of icterus. At no time should the patient be allowed to become dehydrated.

An example of the serious consequences of an inadequate fluid intake is shown in the single fatality in this series. The patient had been able to obtain only a meager supply of water during the week preceding his hospitalization and had a severe diarrhea which further dehydrated him. As a result, a severe bile nephrosis developed, producing irreversible changes in the renal tubules, which undoubtedly contributed to his death.

Since relapses frequently developed in patients who had an intercurrent infection of the respiratory tract, care should be taken to shield the patient from respiratory infections of any type.

#### COMMENT

A comparison of the clinical observations on patients with epidemic hepatitis with those of patients with postvaccinal hepatitis reveals several differences worthy of mention.

Of the patients with postvaccinal hepatitis, as reported by Turner and his co-workers,<sup>13</sup> only an occasional one had fever, whereas fever, chills and evidence of an infectious process was an outstanding feature in 61 per cent of the patients in this group. The incidence of various types of dermatitis in the patients with postvaccinal type of hepatitis was much more frequent than in those with epidemic hepatitis. Only 2 per cent of our patients exhibited any type of dermatitis, in contrast to the high incidence of dermatitis in the postvaccinal group. Lymphadenopathy, frequently pronounced in this series, is not mentioned in the reports on cases of postvaccinal hepatitis. There seemed to be a more frequent tendency for anemia and severe complications to develop in the latter group. Psychic reactions were not observed in any of our patients. It is noteworthy that even in the rapidly fatal case in this series the patient's mental reaction remained clear until he died.

When epidemic hepatitis is compared with catarrhal jaundice, it is apparent that the observations are quite similar. We do not feel that we can distinguish any significant differences between acute infectious (epidemic) hepatitis and catarrhal jaundice. The term "acute infectious" (or "epidemic") hepatitis seems to be preferable to the term "catarrhal jaundice," for describing this disease. The latter term is misleading as there is definite evidence of hepatic parenchymal and hepatocellular involvement and as hepatitis without jaundice is relatively common.

There is no doubt in our minds that this is frequently a serious disease, which by its seemingly benign course may mislead both the patient and

the clinician. A prolonged convalescent period is required before hepatic functional efficiency is restored to normal and the patient is to be considered well.

#### SUMMARY AND CONCLUSIONS

Two hundred and thirty-eight patients with epidemic hepatitis with jaundice and 17 patients with hepatitis without jaundice were studied by various clinical and laboratory methods during the six month period from Nov 16, 1943 to May 16, 1944. A total of 448 patients with hepatitis with jaundice were observed during this period. There was 1 death in this series.

The clinical characteristics of hepatitis without jaundice were studied.

The clinical characteristics of epidemic hepatitis with jaundice were found to be not essentially different from those of catarrhal jaundice.

Clinically, epidemic hepatitis is similar to postvaccinal hepatitis but differs in the frequent occurrence of chills, fever and lymphadenopathy and in the relative absence of dermatitis, anemia and mental reactions.

Fever, chills and other evidence of an acute infectious, systemic disease are common initial symptoms.

The disease is usually mild but has a frequent tendency to relapse with exertion, excessive physical fatigue and intercurrent infections. Relapses can be prevented or minimized by adequate rest in bed and by a prolonged convalescent period.

The disease, although usually benign, may be rapidly fatal. Repeated severe hemorrhages from ulcerations in the gastrointestinal tract and nephrosis due to depositions of bile pigment in the renal tubules were noteworthy complications in the fatal case.

The icterus index, although useful in following the course of the disease, is not a reliable guide in determining either the activity of the hepatitis or the degree of hepatic functional impairment following an attack of epidemic hepatitis. The degree of icterus does not always indicate the severity of hepatic damage.

The hippuric acid test of hepatic function frequently indicates residual hepatic functional impairment long after the icterus index has returned to normal.

The sedimentation rate is useful in determining the residual activity of the hepatitis and frequently remains elevated for several weeks after the icterus index has returned to normal.

A prolonged convalescence and conservative management of the patients are important in treatment.

# Progress in Internal Medicine

## INFECTIOUS DISEASES

ELEVENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

HOBART A. REIMANN, M.D.

PHILADELPHIA

In the preparation of these reviews, during each succeeding year of the war, I have expected my task to be easier because of apparent distractions in investigative work. Instead, there has been an ever increasing amount of important contributions to the knowledge of infections to review. First came studies of many sulfonamide compounds, their modes of administration, their pharmacology and their effect on many infections, then followed the introduction of penicillin, its route of administration, its pharmacology and its effect on various diseases, and now such studies are being made on substances which attack gram-negative bacilli. So rapidly have advances been made that for certain diseases sulfonamide therapy is already regarded as old fashioned and serum therapy is only rarely used. The full import of all these discoveries during the turmoil of war will be even more fully appreciated later. This era is as important as the Pasteur-Koch epoch in the field of infectious diseases.

Advances in knowledge of exotic diseases like malaria, filariasis and typhus have gone apace with the worldwide dispersal of military personnel. Evidence is accumulating that filtrable viruses cause many more diseases than were known of before. Numerous "new" viral infections of the central nervous system and of the respiratory tract are established as entities. Infectious hepatitis is shown to be almost certainly of viral origin, and evidence points to viruses as causes of infections of the gastrointestinal tract and urinary tract, areas heretofore unassociated primarily with viral diseases. At the same time advances were made in the study and control of air-borne infection.

### PENICILLIN

In the month of April 150 billion units of penicillin was allocated for civilian use, in June a total of 650 billion units was made, and for August 800 billion is in prospect. The tremen-

dous decrease of the cost to about 49 cents per 100,000 units makes it doubtful if synthesis on a commercial scale will be attempted. Penicillin will soon be available in tablet and in liquid form for oral administration.

In addition to the great benefits derived therefrom, there is reason to fear<sup>1</sup> that the release of penicillin will be followed by the same abuse, waste and commercialization that followed the release of the sulfonamide compounds. It is perhaps too much to hope that all physicians, druggists, laymen in general and the drug industry will cooperate in the proper use of penicillin. Regulation by some official body may be needed to prevent absurd combinations of penicillin with chewing gum, mouth wash, cough drops, skin lotions and so forth. The use of penicillin pastilles<sup>2</sup> has already been recommended for Vincent's stomatitis and even for diphtheria, for either of which the value of penicillin is doubtful. It has already been suggested, facetiously it is hoped, that a combination of a sulfonamide compound, penicillin and streptomycin will control most infections without need for further diagnoses.

Penicillin is preferable to sulfonamide compounds in the treatment of pneumococcus, hemolytic streptococcus and staphylococcus pneumonia<sup>3</sup> and of pneumococcus meningitis but not of meningococcus meningitis<sup>4</sup>. Penicillin also seems to be of more value and safer than sulfonamide compounds in the treatment of severe

1 Falk, L. A., and Goodman, H. Will Penicillin Be Used Indiscriminately? Correspondence, J. A. M. A. **127** 672 (March 17) 1945.

2 MacGregor, A. B., and Long, D. A. Use of Penicillin Pastilles in Oral Infections. Preliminary Report, Brit. M. J. **2** 686-688 (Nov. 25) 1944.

3 (a) Craig, W. M., and others. Penicillin. A Progress Report Based on 1,455 Cases Treated at the National Naval Medical Center, Bethesda, Maryland, U. S. Nav. M. Bull. **44** 453-479 (March) 1945. (b) Lueck, A. G., and Edge, C. O. Penicillin in Pneumonia, *ibid.* **44** 480-485 (March) 1945.

4 Meads, M., Harris, H. W., Samper, B. A., and Finland, M. Treatment of Meningococcal Meningitis with Penicillin, New England J. Med. **231** 509-517 (Oct. 12) 1944.

<sup>1</sup> From the Jefferson Medical College and Hospital.

infections of the throat caused by hemolytic streptococci. Plummer and his colleagues<sup>5</sup> on several occasions noted the development of hemolytic streptococcus peritonsillar abscess, pneumonia and empyema in patients who were receiving sulfadiazine. With penicillin therapy improvement was usually evident within eight to twelve hours after the first injection of 15 000 units after which injections were then given every four hours. Treatment should be continued for six days lest relapse occur. Hemolytic streptococci disappeared promptly from the nasopharynx but often reappeared after treatment was stopped. These authors recommend the injection of penicillin without delay in case of any serious progressive hemolytic streptococcus infection but not for mild sore throat. Since mild pharyngitis occurs during many other infectious diseases not associated with the hemolytic streptococcus much penicillin will be wasted unless cultures are made in each instance before therapy. No one by inspection alone can make an accurate diagnosis of a strep throat. Group D hemolytic streptococci are much more resistant to the action of penicillin than those of other groups.<sup>6</sup>

Further experience leads Spink<sup>7</sup> who once strongly favored the use of sulfonamide compounds for staphylococcal infections, to write that penicillin is the more effective therapeutic agent. The same conclusion concerning the use of penicillin applies to certain infections caused by hemolytic streptococci. Evidence of the development of resistance of staphylococci to penicillin appeared in his studies.

The value of penicillin in surgery is discussed in the July 1944 issue of the *British Journal of Surgery*. According to Meleney,<sup>8</sup> penicillin may be expected to give good results in 75 per cent of cases of grave infection by hemolytic streptococci but less often when mixed infection is present.

*For Subacute Bacterial Endocarditis*—Reports of an exhaustive study of subacute bacterial

endocarditis by Kelson and White appears in the January 1945 issue of the *Annals of Internal Medicine*. Studies were made before and after the advent of sulfonamide drugs and penicillin. Before 1939 no treatment was effective and all of 245 patients studied died from the disease, the patient surviving longest lived nineteen months after the onset. After sulfonamide therapy was introduced 7 (19 per cent) of 79 patients recovered. Seventeen of the treated patients received heparin in addition, 3 of these recovered. Of 9 patients given large doses of penicillin 6 (67 per cent) have shown "a definite control (perhaps a cure)," but up to the time of publication of the report only eight months had elapsed. Further study is necessary. Dawson and Hunter<sup>9</sup> also report promising results in the treatment of 27 patients of whom 21 were greatly benefited for a period of many months. These and other authors, including me, are not sure that heparin is needed as an adjuvant in the treatment. The arbitrary dosage of penicillin they recommend is 200,000 units daily for three weeks. Larger or smaller amounts may be needed. The intramuscular drip method of administration is recommended. Paullin and McLaughlin<sup>10</sup> report 3 "cures" among 6 patients and others<sup>11</sup> 7 among 9 patients. According to Loewe<sup>12</sup> if the patient is in good physical condition the duration of the disease less than three months and the causative organism sensitive to penicillin a satisfactory result may be expected barring accidents "in virtually every case." While this statement may be true, it must be remembered that the injured valve remains even after "cure" and the ubiquitous *Streptococcus viridans* is ready for reinvasion when opportunity is favorable.

An interesting but little emphasized sidelight emerged from one study, namely that dental extraction was second only to infections of the upper respiratory tract as an inciting cause of the disease. A history of recent dental operations was given in 25 per cent of cases.

In an editorial comment<sup>13</sup> on some of these studies it is stated that it is not yet possible to

5 Plummer, N. A., and others. Penicillin Therapy in Hemolytic Streptococcal Pharyngitis and Tonsillitis, *J. A. M. A.* **127**:369-374 (Feb. 17) 1945.

6 Watson, R. F. Sensitivity of Various Serological (Lancefield) Groups of Streptococci to Penicillin, *Proc. Soc. Exper. Biol. & Med.* **57**:65-69 (Oct.) 1944.

7 Spink, W. W., and Hall, W. H. Penicillin Therapy at the University of Minnesota Hospitals 1942-1944, *Ann. Int. Med.* **22**:511-525 (April) 1945. Spink, W. W., Hall, W. H., and Ferris, V. Clinical Significance of Staphylococci with Natural or Acquired Resistance to Sulfonamides and to Penicillin, *J. A. M. A.* **128**:555-559 (June 23) 1945.

8 Meleney, F. L. Recent Experiences with Penicillin in the Treatment of Surgical Infections, *Bull. New York Acad. Med.* **20**:517-537 (Oct.) 1944.

9 Dawson, M. H., and Hunter, T. H. The Treatment of Subacute Bacterial Endocarditis with Penicillin, *J. A. M. A.* **127**:129-137 (Jan. 20) 1944.

10 Paullin, J. E., and McLaughlin, C. J. The Treatment of Subacute Bacterial Endocarditis with Penicillin, *Ann. Int. Med.* **22**:475-484 (April) 1945.

11 Meads, M., Harris, H. W., and Finland, M. The Treatment of Bacterial Endocarditis with Penicillin, *New England J. Med.* **232**:463-474 (April 20) 1945.

12 Loewe, L. The Combined Use of Anti-Infectious and Anticoagulant Agents in the Treatment of Subacute Bacterial Endocarditis, *Bull. New York Acad. Med.* **21**:59-86 (Feb.) 1945.

13 Treatment of Subacute Bacterial Endocarditis, editorial, *Ann. Int. Med.* **27**:131-133 (Jan.) 1945.

reach a definite conclusion as to the efficacy of the measures tested or whether heparin is of added value or not. The procedures are still in the experimental stage. Nevertheless, penicillin is by far the most effective agent ever used for the treatment of subacute bacterial endocarditis.

*For Various Other Diseases*—Penicillin was of value in the treatment of ornithosis or psittacosis,<sup>14</sup> yaws,<sup>15</sup> and rat bite (*Streptobacillus moniliformis*) fever.<sup>16</sup> Anthrax<sup>17</sup> was apparently controlled, although the bacillus is relatively resistant in the test tube. Penicillin caused great improvement in the pustular eruption of smallpox after sulfathiazole had failed.<sup>18</sup> Conflicting reports concern its value for leptospirosis; in one paper<sup>19</sup> no beneficial effects were noted, and in two others<sup>20</sup> it was reported that improvement seemed to depend on its use. Penicillin was effective in treating artificially infected guinea pigs,<sup>21</sup> mice and hamsters.<sup>22</sup> In the study on mice and hamsters, penicillin and specific immune serum seemed to have equal therapeutic values.

In treatment of experimental syphilis in rabbits, even large doses were not sufficient to kill all the spirochetes, although the primary lesions healed satisfactorily.<sup>23</sup> In treatment of human

syphilis, British workers<sup>24</sup> record immediate favorable responses in all cases of early infections. If one judges by later effects, the arsenical compounds and bismuth might have given better results. The doses used were 30,000 units intramuscularly every three hours for eighty injections, or 2,400,000 units in ten days, or 30,000 units every hour for forty injections (1,200,000 units). The need for frequent injections makes routine treatment inconvenient. Excellent immediate results are reported<sup>25</sup> in the treatment of acute syphilitic meningitis with 600,000 to 4,000,000 units of penicillin given over a period of eight to sixteen days. It is still too early to be able to predict the later course of the infection.

Penicillin has no beneficial effect in the treatment of viral pneumonia,<sup>26</sup> rheumatoid arthritis,<sup>26</sup> tularemia,<sup>27</sup> leprosy,<sup>28</sup> tetanus<sup>29</sup> or of inoculation malaria.<sup>30</sup> Penicillin was without effect on the multiplication of the viruses of vaccinia, St. Louis encephalitis and equine encephalitis; it did inhibit the growth of the "viruses" of psittacosis and mouse meningopneumonitis in chick embryos, but such great amounts were required as to render its practical importance doubtful.<sup>31</sup> However, 2 recorded patients<sup>14</sup> and 1 of my own with psittacosis seemed to be benefited by penicillin. The clinical value of penicillin, as in the case of anthrax, cannot always be judged by its action on the experimental animal or in the test tube.

Penicillin gives little or no benefit to patients with bronchiectasis.<sup>32</sup> It is helpful for chronic bronchitis, often immediately so, causing a disappearance of cough and sputum. Inhaled nebu-

14 Turgasen, F. E. Human Ornithosis Treated with Penicillin, *J. A. M. A.* **126** 1150-1151 (Dec 30) 1944. Flippin, H. F., Gaydos, M. J., and Fittipaldi, W. V. Penicillin for Human Psittacosis, *ibid.* **127** 280-281 (May 26) 1945.

15 Whitehill, R. C., and Austrian, R. Treatment of Primary and Secondary Yaws with Penicillin, *Bull. Johns Hopkins Hosp.* **75** 232-240 (Oct) 1944.

16 Altemeier, W. A., Snyder, H., and Howe, G. Penicillin Therapy in Rat Bite Fever, *J. A. M. A.* **127** 270-273 (Feb 3) 1945.

17 Murphy, F. D., LaBocchetta, A. C., and Lockwood, J. S. Treatment of Human Anthrax with Penicillin, *J. A. M. A.* **126** 948-950 (Dec 9) 1944.

18 Jeans, W. D., Jeffrey, J. S., and Gunders, K. Penicillin and Smallpox. Report of Four Cases, *Lancet* **2** 44-46 (July 8) 1944.

19 Bulmer, E. Weil's Disease in Normandy. Its Treatment with Penicillin, *Brit. M. J.* **1** 113-114 (Jan 27) 1945.

20 Hart, V. L. A Case of Weil's Disease Treated with Penicillin, *Brit. M. J.* **2** 720 (Dec 2) 1944. Cross, R. M. Penicillin in Weil's Disease, *Lancet* **1** 211-212 (Feb 17) 1945.

21 Alston, J. M., and Broom, J. C. The Action of Penicillin on *Leptospira* and on Leptospiral Infections in Guinea Pigs, *Brit. M. J.* **2** 718-719 (Dec 2) 1944.

22 Larson, C. L., and Griffiths, J. J. A Comparison of the Effect of Penicillin and Immune Serum in the Treatment of Experimental Leptospirosis in Young White Mice and in Hamsters, *Pub. Health Rep.* **66** 317-323 (March 23) 1945.

23 Ercoli, N., and Lafferty, L. C. The Anti-Spirochetal Activity of Penicillin in Experimental Infections, *Proc. Soc. Exper. Biol. & Med.* **57** 4-6 (Oct) 1944.

24 Ross, A. O. F., and others. Treatment of Early Syphilis with Penicillin, *Lancet* **2** 845-848 (Dec 30) 1944.

25 Nelson, R. A., and Duncan, L. Acute Syphilitic Meningitis Treated with Penicillin, *Bull. Johns Hopkins Hosp.* **75** 327-352 (Dec) 1944.

26 Boland, E. W., Headley, N. E., and Hench, P. S. The Effect of Penicillin on Rheumatoid Arthritis, *J. A. M. A.* **126** 820-823 (Nov 25) 1944.

27 Josey, A. I. Penicillin Treatment of a Case of Tularemia Without Effect, *J. A. M. A.* **126** 496-497 (Oct 21) 1944.

28 Faget, G. H., and Pogge, R. C. Penicillin Treatment of Leprosy. Clinical Note, *Pub. Health Rep.* **60** 324-325 (March 23) 1945.

29 Buxton, R., and Kurman, R. L. Tetanus. Report of Two Cases Treated with Penicillin, *J. A. M. A.* **127** 26 (Jan 6) 1945.

30 Hindle, J. A., Rose, A. S., Trevett, L. D., and Prout, C. The Effect of Penicillin on Inoculation Malaria. A Negative Report, *New England J. Med.* **232** 133-136 (Feb 1) 1945.

31 Parker, R. F., and Diefendorf, H. W. Effect of Penicillin on Certain Viruses, *Proc. Soc. Exper. Biol. & Med.* **57** 351-354 (Dec) 1944.

32 Stookey, P. F., and others. Penicillin Therapy in Bronchiectasis, *South. M. J.* **38** 98-102 (Feb) 1945.

lized penicillin caused improvement in 5 of 20 patients studied by others<sup>33</sup> Simplified methods for the clinical measurement of penicillin in the blood and the determination of the sensitivity of bacteria to it are described<sup>34</sup>

In a study of reasons for the failure of penicillin to cure certain diseases, Bloomfield and his co-workers<sup>35</sup> classify them as follows: (a) insufficient dosage, (b) insufficient surgical drainage, (c) overwhelming infection or lack of resistance even to penicillin-sensitive bacteria and (d) progression of other conditions (for example nephritis) penicillin fastness is apparently of little importance

*Methods of Administration*—*Oral Therapy* Penicillin may be given orally Some of it is lost in the intestinal tract, but if the doses given are large as compared with those used for parenteral injection, satisfactory amounts may be attained in the blood According to McDermott's<sup>36</sup> group, about five times as much must be given orally to obtain levels comparable to those obtained after intramuscular injection In another study<sup>37</sup> it was reported that 1.5 to 7 Gm of trisodium citrate given with penicillin two hours after breakfast greatly increases its absorption According to Gyorgy and his co-workers,<sup>38</sup> penicillin calcium given orally with trisodium citrate was as effective in the treatment of gonorrhea as the same dose given parenterally Oral administration of 250,000 to 300,000 units over a period of sixteen to twenty hours gave good results British investigators<sup>37b</sup> used with success the combined stabilizing effect of egg albumin and the buffer action of sodium bicarbonate, and others<sup>39</sup> used cottonseed oil After a single

dose of 90,000 units, the amounts in the blood reached 0.05 units in one hour and lasted four hours, which is about the level usually attained in clinical practice after the intramuscular injection of 20,000 units Possible advantages of oral therapy are slower absorption, its longer duration in the blood and the fact that the product used need not be highly purified A disadvantage might be the tendency to indiscriminate use and a waste of material, as with the sulfonamide compounds

Penicillin given rectally in suppositories appears in the blood in effective amounts<sup>40</sup>

*Parenteral Therapy* Penicillin injected intramuscularly is demonstrable in the blood for longer periods if the vehicle is a 5 per cent solution of dextrose instead of an isotonic solution of sodium chloride<sup>41</sup> Penicillin can be kept in the blood longer if epinephrine hydrochloride is injected intramuscularly with it<sup>42</sup> and also if a combination of penicillin with human plasma, making a penicillin-protein complex, is given intravenously<sup>43</sup>

*Inhalation Therapy* Barach and his aids<sup>33</sup> investigated the usefulness of inhaled, nebulized penicillin aerosol for the treatment of pulmonary infection When inhaled, penicillin appears in small amounts in the blood, but the aim was not so much to obtain large amounts in the blood as large amounts locally Perhaps combined parenteral injection and inhalation therapy is desirable for the treatment of pulmonary abscess, bronchiectasis or other bronchial infections British observers<sup>44</sup> feel that inhalation therapy with penicillin has a number of advantages because it obviates oft repeated injections, especially for infants, and because penicillin is so rapidly excreted when administered otherwise

33 Barach, A. L., and others. Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess. Preliminary Report, *Ann Int Med* **22**: 485-509 (April) 1945

34 Cooke, J. V. A. Simple Clinical Method for the Assay of Penicillin in Body Fluids and for Testing of Penicillin Sensitivity of Bacteria, *J A M A* **127**: 445-449 (Feb 24) 1945

35 Bloomfield, A. L., Kirby, M. M., and Armstrong, C. D. A Study of "Penicillin Failures," *J A M A* **126**: 685-691 (Nov 11) 1944

36 McDermott, W., Bunn, P. A., Benoit, M., DuBois, R., and Haynes, W. Oral Penicillin, *Science* **101**: 228-229 (March 2) 1945

37 (a) Charney, J., Alburn, H. E., and Bernhart, F. W. Urinary Excretion of Penicillin in Man After Oral Administration with Gastric Antacids, *Science* **101**: 251-253 (March 9) 1945. (b) Little, C. D. H., and Lumb, G. Penicillin by Mouth, *Lancet* **1**: 203-206 (Feb 17) 1945

38 Gyorgy, P., and others. Administration of Penicillin by Mouth, *J A M A* **127**: 639-642 (March 17) 1945

39 Libby, R. L. Oral Administration of Penicillin in Oil, *Science* **101**: 178-180 (Feb 16) 1945

40 Loewe, L., and others. Administration of Penicillin by Rectal Suppository, *J A M A* **128**: 18 (May 5) 1945

41 Armstrong, C. D., Halpern, R. M., and Cutting, W. C. Prolongation of the Action of Penicillin After Intramuscular Injection, *Proc Soc Exper Biol & Med* **58**: 74-76 (Jan) 1945

42 Fisk, R. T., Foord, A. G., and Alles, G. Prolongation of Penicillin Activity by Means of Adrenalin, *Science* **101**: 124-125 (Feb 2) 1945

43 Chow, B. F., and McKee, C. M. Interaction Between Crystalline Penicillin and Human Plasma Proteins, *Science* **101**: 67-68 (Jan 19) 1945. Inactivation of the Antibiotic Activity of Penicillin by Cysteine Hydrochloride. I. Clinical Aspects of Inactivation, *Proc Soc Exper Biol & Med* **58**: 175-177 (Feb) 1945. Cavallito, C. J., and Bailey, J. H. Preliminary Note on the Inactivation of Antibiotics, *Science* **100**: 390 (Oct 27) 1944

44 Knott, F. A., and Clark, W. H. Absorption of Aerosol Penicillin via the Lungs, *Lancet* **1**: 468-469 (April 14) 1945

*Bacteriologic Studies of Resistance to Penicillin*—*Escherichia coli*,<sup>45</sup> *Eberthella typhosa*, *Bacillus proteus* and *Salmonella*<sup>46</sup> are not as resistant to the effect of penicillin as was once thought. Furthermore, their susceptibility can be increased by adding methionine and normal serum to the culture medium. From cultural experiments on *Esch. coli* and *Salmonella* in synthetic medium rather than in meat infusion broth, it appeared that casein hydrolysate, asparagine, glutamic acid and other amino acids partially antagonize the effect of penicillin. The resistance of gram-negative bacilli to penicillin therefore seems at least to some extent, to be extrinsic in nature.

Different strains of staphylococci, according to Neter,<sup>47</sup> vary in their susceptibility to penicillin, tyrothricin and streptomycin in culture medium. Their susceptibility to the effects of one antibiotic is not always the same as that to the effects of another. If the same variation occurs in the body during infection, it would be desirable beforehand to determine and to select the most effective antibiotic agent for treatment. Staphylococci may become resistant to both sulfonamide compounds and penicillin.<sup>7</sup>

According to Demerec,<sup>48</sup> induced resistance of a strain of staphylococcus to penicillin results from the appearance of variant forms, which survive because they are resistant while the sensitive forms disappear. Resistance itself is not related to pathogenicity,<sup>49</sup> and the course of infection proceeds regardless of changes in resistance to penicillin. Gallardo, like Spink, found about 13 per cent of pathogenic strains of staphylococci to be naturally resistant to penicillin, another 9 per cent become resistant during treatment with penicillin. The resistance which bacteria develop against penicillin, especially if developed in vitro, may not be permanent. Two strains of staphylococci which became resistant rapidly lost this property on further subculture

in broth.<sup>50</sup> It is probable that penicillin-sensitive variants reappear in culture mediums. Gonococci may become resistant to penicillin by growth in a medium containing it.<sup>51</sup> Morphologic changes as well as differences in fermentation reactions appeared in the resistant forms.

Kirby<sup>52</sup> shows that resistant staphylococci produce a penicillin-inactivating substance, but the staphylococci themselves are inhibited by penicillin and will not survive unless great numbers are present. In contrast with other bacteria staphylococci are said to disintegrate when subjected to penicillin, the lysed cellular elements may be partly responsible for the fever and toxicity of infections which these bacteria cause. According to Todd<sup>53</sup> however, all penicillin-sensitive micro-organisms are susceptible to bacteriolysis by penicillin.

*Other Studies on Penicillin*—Penicillin is inactivated by cysteine, it also combines with human serum albumin<sup>43</sup> and, contrary to previous views, is inactivated in varying degrees by contact with human blood<sup>54</sup> when certain bacteria are used as test organisms, probably owing to the presence in the blood of penicillinase produced by penicillin-resistant bacteria. Penicillin is both bacteriostatic and bactericidal at temperatures as high as 42 C.<sup>55</sup> It is doubtful if it acts only on dividing cells.

The mode of action of penicillin on bacterial growth is as hard to understand as is the action of the sulfonamide compounds.<sup>56</sup> Penicillin is bactericidal, but even in a culture of bacteria mixed with penicillin there are almost always a few surviving or visible bacteria. This persistence is explained on the basis of the appearance and survival of penicillin-resistant variants. One theory, perhaps too simple to account for the bactericidal effect, assumes that penicillin prevents cell division but not cell growth, the cell increases in size and bursts. Lysis of bac-

45 Schwartzman, G. (a) Inhibition of *E. coli* by Penicillin, *Science* **100** 477-478 (Nov 24) 1944, (b) On the Nature of Refractiveness of Certain Gram-Negative Bacilli to Penicillin, *ibid* **101** 276-277 (March 16) 1945.

46 Steiner, M. Gram-Negative Bacilli Susceptibility to Penicillin, *U. S. Nav. M. Bull.* **44** 486-493 (March) 1945.

47 Neter, E. Relative Susceptibility of Staphylococci to the Bacteriostatic Action of Antibiotics, *Proc. Soc. Exper. Biol. & Med.* **58** 126-128 (Feb.) 1945.

48 Demerec, M. Production of Staphylococcus Strains Resistant to Various Concentrates of Penicillin, *Proc. Nat. Acad. Sci.* **31** 16-20 (Jan.) 1945.

49 Gallardo, E. Sensitivity of Bacteria from Infected Wounds to Penicillin. II. Results in 112 Cases, *War Med.* **7** 100-110 (Feb.) 1945.

50 Todd, E. W., Turner, G. S., and Drew, L. G. W. The Temporary Character of "Fastness" of Staphylococci to Penicillin, *Brit. M. J.* **1** 111-113 (Jan 27) 1945.

51 Bahn, J. M., Ackerman, H., and Carpenter, C. M. Development in Vitro of Penicillin-Resistant Strains of *Gonococcus*, *Proc. Soc. Exper. Biol. & Med.* **58** 21-24 (Jan.) 1945.

52 Kirby, W. M. M. Bacteriostatic and Lytic Actions of Penicillin on Sensitive and Resistant Staphylococci, *J. Clin. Investigation* **24** 165-169 (March) 1945.

53 Todd, E. N. Bacteriolytic Action of Penicillin, *Lancet* **1** 74-77 (Jan 20) 1945.

54 Bigger, J. W. Inactivation of Penicillin by Serum, *Lancet* **2** 400-402 (Sept 23) 1944.

55 Garrod, L. P. Action of Penicillin on Bacteria, *Brit. M. J.* **1** 107-110 (Jan 27) 1945.

56 How Penicillin Works, *Lancet* **1** 276-277 (March 3) 1945.

teria is commonly observed in the presence of penicillin. Perhaps penicillin kills bacteria with a minimum of disturbance to the bacterial protoplasm so that autolysis takes place readily.

Taxonomists may be alarmed by the report of one hundred new strains or "mutations" arising from a strain of *Penicillium notatum* after bombardment with neutrons.<sup>57</sup> The idea back of the experiment was to induce the appearance of variant forms which may be even better producers of penicillin than the parent form. The appearance of so many variant forms suggests that the phenomenon of microbial variation is far more complex than is usually believed, as indicated also by earlier studies on *Micrococcus tetragenus* (*Gafkya tetragenus*) in which more than twenty variants appeared.

#### STREPTOMYCIN AND OTHER ANTIBIOTICS

Although increasingly pure preparations of penicillin inhibit the growth of many gram-negative bacilli,<sup>58</sup> the effectiveness is not great enough to promise beneficial therapeutic results in infections they cause. Accordingly, attention is now being given to streptomycin, an extract of *Actinomyces griseus*, similar in many respects to streptothricin.<sup>59</sup> Streptomycin has the advantage of higher potency against certain pathogenic bacilli; it is not decomposed by any bacteria so far tested, and it is not toxic for the host. At present streptomycin is effective against a number of diseases caused by gram-negative bacilli in animals:<sup>60</sup> tularemia, tuberculosis and infections with Friedlander's bacillus (*Klebsiella pneumoniae*). It is of less value than penicillin for infections with *Borrelia novyi* and with *Leptospira icterohaemorrhagiae*.<sup>61</sup>

Thus far not enough patients with systemic infections have been treated with streptomycin to permit a judgment of its value, but the results are promising. Recovery took place during treatment of 4 of 7 patients with typhoid.<sup>62</sup> The fact that amounts appeared in the blood greater than those needed to kill the bacteria in culture suggests that streptomycin aided in recovery. The results obtained were less impressive than the results of penicillin therapy for certain other diseases. No explanation is available to account for the failures except that unknown factors in the body may protect the bacilli from the drug or may interfere with its action.

At a recent conference at Rahway, N. J., promising results were reported by Foshay in the treatment of tularemia: a few patients with brucellosis seemed to have been helped, but, again as in typhoid, others were not. Because streptomycin given parenterally is largely excreted in the urine, it is effective in many instances in eliminating *Esch. coli*, *B. proteus* and *Bacillus pyocyaneus* from the urine, but only if the bacteria present happen to be sensitive to drugs.<sup>63</sup> Streptomycin given orally is almost all excreted in the feces. Here, it successfully suppresses or eliminates *Esch. coli* and other bacteria if they are drug sensitive. When given parenterally, theoretically sufficient amounts appear in the spinal fluid, but no evidence of benefit was obtained in patients with tuberculous meningitis.<sup>64</sup> The effects on *Hemophilus influenzae* meningitis were unimpressive, as were those on pulmonary tuberculosis. Yet in experimental animals, streptomycin was of greater value than any substances yet tested for tuberculosis. Reports of the use of streptomycin in treating cholera, plague and bacillary dysentery are eagerly anticipated.

Crystalline preparations of both streptomycin and streptothricin have been made.<sup>64</sup>

Energetic search is under way to test the ability of many species of fungi to make antibiotic substances. Some of them already give indication of being effective against certain filtrable viruses.<sup>65</sup> A new substance, chaetomin, which is active principally against gram-positive bacteria,

57 Myers, W. G., and Hanson, H. J. New Strains of *Penicillium Notatum* Induced by Bombardment with Neutrons, *Science* **101** 357-358 (April 6) 1945.

58 Hobby, G. L. The Antibacterial Action of Penicillin Against Gram-Negative Organisms, *Science* **100** 500-501 (Dec 1) 1944. Shwartzman.<sup>45a</sup>

59 Waksman, S. A., Bugie, E., and Schatz, A. Isolation of Antibiotic Substances from Soil Microorganisms, with Special Reference to Streptomycin and Streptothricin, *Proc. Staff Meet., Mayo Clin.* **17** 537-548 (Nov 15) 1944.

60 Heilman, F. R. Streptomycin in the Treatment of Experimental Tularemia, *Proc. Staff Meet., Mayo Clin.* **19** 553-559 (Nov 29) 1944. Feldman, W. H., and Hinshaw, H. C. Effects of Streptomycin in Experimental Tuberculosis in Guinea Pigs, *ibid.* **19** 593-599 (Dec 27) 1944. Heilman, F. R. Streptomycin in the Treatment of Experimental Infection with Microorganisms of the Friedlander Group (*Klebsiella*), *ibid.* **20** 33-39 (Feb 7) 1945.

61 Heilman, F. R. Streptomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis *icterohaemorrhagiae* (Weil's Disease), *Proc. Staff Meet., Mayo Clin.* **20** 169-176 (May 30) 1945.

62 Reimann, H. A., Elias, W. F., and Price, A. H. Streptomycin for Typhoid Fever. A Pharmacologic Study, *J. A. M. A.* **128** 175-180 (May 19) 1945.

63 Reimann, H. A., Price, A. H., and Elias, W. F. To be published.

64 Fried, J., and Wintersteiner, O. Crystalline Reineckates of Streptothricin and Streptomycin, *Science* **101** 613-615 (June 15) 1945.

65 Jones, D., Baudette, F. R., Geiger, W. B., and Waksman, S. A. A Search for Virus-Inactivating Substances Among Microorganisms, *Science* **101** 665-668 (June 29) 1945.

has been prepared.<sup>66</sup> Antibiotics derived from *Aspergillus* are active against the tubercle bacillus but not against staphylococci.<sup>67</sup> Russians isolated a substance called gramicidin S, which inhibits the growth of a variety of both gram-positive and gram-negative bacteria.<sup>68</sup> In one study, tyrothricin sprayed twice daily into the throats of carriers had no effect in eliminating hemolytic streptococci.<sup>69</sup>

The juice and steam distillate of juice of buttermilk<sup>70</sup> is strongly antibiotic for a number of pathogenic gram-positive and gram-negative bacteria, for *Mycobacterium tuberculosis* and for certain yeasts. Certain chemicals, among them urethane (butyl carbamate),<sup>71</sup> are bacteriostatic and bactericidal for gram-negative bacteria and to some extent for gram-positive ones. They are said to be of value in the treatment of infections caused by gram-negative bacteria. Another compound, 2,4-dichlorophenoxyacetic acid, retards certain gram-positive bacteria.<sup>72</sup>

Attempts at the synthesis of antibiotics are in progress, and success has been reported in the preparation of an isomer of clavacin.<sup>73</sup> Even if penicillin itself is eventually synthesized, one wonders whether the cost of it will be lower than that of the natural penicillin now made.

66 Waksman, S. A., and Bugie, E. Chaetomin, a New Antibiotic Substance Produced by *Chaetomium Chochliodes*, *J. Bact.* **48** 527-530 (Nov.) 1944.

67 Soltys, M. A. Antibiotic Action of *Aspergillus Fumigatus* Against *Mycobacterium Tuberculosis*, *Nature*, London **154** 550-551 (Oct. 28) 1944. Asheshov, I. N., and Strelitz, F. An Antibiotic Substance Active Against *Mycobacterium Tuberculosis*, *Science* **101** 119-120 (Feb. 2) 1945.

68 Sergiev, P. G. Clinical Use of Gramicidin S, *Lancet* **2** 717-719 (Dec. 2) 1944. Gause, G. F., and Brazhnikova, M. G. Gramicidin "S", Its Origin and Mode of Action, *Am. Rev. Soviet Med.* **2** 134-138 (Dec.) 1944.

69 Hartley, G., Enders, J. F., Mueller, J. H., and Schoenbach, E. B. Absence of Clinical Disease in Spite of a High Incidence of Carriers of Group A Hemolytic Streptococci of a Single Type. Failure of Tyrothricin to Influence the Carrier Rate, *J. Clin. Investigation* **24** 92-96 (Jan.) 1945.

70 Seegal, B. C., and Holden, M. The Antibiotic Activity of Extracts of Ranunculaceae, *Science* **101** 413-414 (April 20) 1945.

71 Weinstein, L., and MacDonald, A. The Effect of Urea, Urethane and Other Carbamates on Bacterial Growth, *Science* **101** 44-45 (Jan. 12) 1945.

72 Stevenson, E. C., and Mitchell, J. W. Bacteriostatic and Bactericidal Properties of 2, 4 Dichlorophenoxyacetic Acid, *Science* **101** 642-644 (June 22) 1945.

73 (a) Puetzer, B., Nield, C. H., and Barry, R. H. The Synthesis of a Clavacin Isomer, *Science* **101** 307-308 (March 23) 1945. (b) Warren, H. A. Sulfadiazine Prophylaxis of Acute Infectious Diseases, *J. Indiana M. A.* **37** 447-451 (Sept.) 1944. (c) Hodges, R. G. The Use of Sulfadiazine as a Prophylactic Against Respiratory Disease, *New England J. Med.* **231** 817-820 (Dec. 21) 1944.

# CHLMOIHLRAPY

*Sulfonamide Prophylaxis of Diseases of the Respiratory Tract*—Glowing accounts of experience in the field of sulfonamide prophylaxis continue to appear. Both Warren and Hodges<sup>73b,c</sup> report striking decrease in the incidence of infections caused by hemolytic streptococci among about 10,000 men in each study who received 1 Gm of sulfadiazine daily. While Warren<sup>73b</sup> and Coburn<sup>74</sup> report no effect on diseases caused by filterable viruses, Hodges<sup>73c</sup> records a diminution in these as well. In two other studies,<sup>75</sup> sulfadiazine prophylaxis was used to prevent implantation of the hemolytic streptococcus on the mucous membrane and to control air-borne infection with this bacterium. In reading Coburn's report<sup>75a</sup> of observations on 600,000 subjects, one wonders how much hyperbole is involved when he writes "Without chemoprophylaxis to prevent implantation of respiratory pathogens, the training programs of the U. S. Navy would have been impossible of maintenance." Mild reactions to sulfadiazine occurred in 0.5 per cent and severe reactions in 0.01 per cent, and 14 deaths probably related to the drug occurred. Similar statistics come from an Army source.<sup>76</sup> Sensitization to the drug did not appear to result from the small doses used prophylactically, and drug resistance of the streptococci did not develop, but in one camp hemolytic streptococci of types 17 and 19 were found to be resistant. Carter<sup>77</sup> states that at one place the incidence of scarlet fever, which varied between 63 and 171 per thousand, fell to 0 two weeks after prophylaxis began, tonsillitis fell from 426 to 46, and rheumatic fever from 87 per thousand to 0. He estimates that between \$50,000,000 and \$100,000,000 were saved by the procedure.

In a series of papers in the January issue of the *Annals of Internal Medicine*, Juhanelle and Siegel report the effects of sulfonamide prophylaxis on acute infections of the respiratory tract. They gave sulfadiazine during fifteen weeks in the winter months to children in an

74 Coburn, A. F. Mass Sulfadiazine Prophylaxis of Respiratory Infections in the U. S. Navy, *Bull. New York Acad. Med.* **21** 281-301 (June) 1945.

75 (a) Coburn, A. F. The Control of Streptococcus Hemolyticus, *Mil. Surgeon* **96** 17-40 (Jan.) 1945. (b) Hodes, H. L., Schwentker, F. F., Chenoweth, B. M., and Peck, J. L. Scarlet Fever as an Air-Borne Infection, *Am. J. M. Sc.* **209** 64-69 (Jan.) 1945.

76 Lee, R. V. Reactions Following Mass Administration of Sulfadiazine, *J. A. M. A.* **126** 630-631 (Nov. 3) 1944.

77 Carter, T. J. Mass Chemoprophylaxis at All Naval Training Stations, *J. A. M. A.* **127** 96 (Jan. 13) 1945.

institution, first 1 Gm daily and then 2 Gm daily, each child receiving a total of 148 Gm. Although mild infections of the respiratory tract and pneumonia were uncommon during this time, the number of attacks and the severity of both diseases were the same in the treated as in the control group. Purulent nasal discharge was the same in each group. Chickenpox also occurred equally in both. Toxic effects were negligible. The effects of sulfonamide drugs on the bacterial flora of the throat were of interest. The most striking was the rapid disappearance of gram-negative cocci and their gradual return even during treatment, those which reappeared had acquired tolerance for the drug. Hemolytic streptococci were only slightly affected. The presence of the indifferent and gamma streptococci in the throats of both the subjects and the controls indicated that these forms of the organism were uninfluenced by the drug. Of interest was the response of pneumococci. These, numerically at least, remained constant during treatment, but changes in the types present were striking. Although numerous types of pneumococci were present before treatment in the treated group and remained unchanged in the untreated group, those of the treated group changed greatly during therapy. Many of the types present before treatment disappeared, to be replaced almost entirely by types XI and XVIII. This change can be accounted for by the fact that pneumococci highly susceptible to the effects of sulfadiazine die off and others which are originally resistant or which develop resistance to the drug remain. Pneumococci which develop a high degree of resistance are unchanged in virulence or type specificity. After treatment is discontinued the distribution of types present before treatment returns.

A disturbing fact was that certain strains of bacteria which developed resistance to the drug in treated subjects were transmitted to children in the control groups.<sup>78</sup> Continuous sulfadiazine therapy was particularly accompanied with the appearance and spread of two drug-resistant strains, type 11 and type 18A. After therapy was discontinued, these types diminished in number but were still present in a few carriers for fourteen months. The development and spread of such drug-resistant pneumococci would be a hazard were it not for penicillin. As in studies on the hemolytic streptococcus discussed last year, the authors suggest that pneumococcal

infection is precipitated not so much by the person's own normal bacterial residents as by new types suddenly acquired from outside sources.

Different results were obtained by other investigators<sup>79</sup> who, after using sulfonamide compounds in treatment, found sulfonamide-resistant pneumococci far less often than they expected to. Apparently none of the strains tested in their cases became resistant during treatment. Of the strains of pneumococci found before sulfonamide therapy, about 30 per cent persisted. As in studies previously mentioned, types of pneumococci not present before appeared during and after treatment.

In a paper by Plummer and others,<sup>5</sup> penicillin is judged to be more effective than sulfonamide compounds in the treatment of hemolytic streptococcus infection of the throat. In the author's experience severe infection caused by these bacteria occasionally occurred during treatment with sulfadiazine.

*Treatment of Acute Infections of the Upper Respiratory Tract with Sulfonamide Compounds*—According to Cecil,<sup>80</sup> neither the sulfonamide drugs nor penicillin are indicated in treating ordinary coryza or grip. They may be useful in rare instances when complications caused by drug-sensitive bacteria are present. For these, penicillin may entirely replace the sulfonamide compounds.

*Sulfonamide Prophylaxis in Oral Surgery*—Bacteremia occurred in 25 of 30 patients (83 per cent) immediately after extraction of teeth, in Pressman and Bender's<sup>81</sup> experience. *Str. viridans* was most often present, *Staphylococcus albus*, the pneumococcus and the nonhemolytic streptococcus, occasionally. Of patients treated with sulfanilamide before extraction of teeth, 23 out of 30 (77 per cent) were found to have organisms in the blood on culture. Sulfanilamide obviously exerted no immediate quantitative effect on bacteria but reduced the numbers present in ten minutes. There was, however, some immediate qualitative effect. Aerobically sulfanilamide exerts no bacteriostatic effect on *Str. viridans*, but it does anaerobically. In another

79 Goodwin, R. A., Wilcox, C., and Finland, M. Persistence of Pneumococci in Sulfonamide Treated Cases of Pneumonia, *Am J M Sc* **209** 628-639 (May) 1945.

80 Cecil, R. L. Chemotherapy in Acute Upper Respiratory Infections, *Bull New York Acad Med* **21** 263-277 (May) 1945.

81 Pressman, R. S., and Bender, I. B. Effect of Sulfonamide Compounds on Transient Bacteremia Following Extracting of Teeth. I. Sulfanilamide, *Arch Int Med* **74** 346-353 (Nov) 1944.

78 Siegel, M., Karr, H. V., and Julianette, L. A. The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides. V. Carrier Epidemic of Sulfonamide-Resistant Pneumococci, *Am J Hyg* **41** 228-241 (March) 1945.

study,<sup>82</sup> subacute bacterial endocarditis followed the extraction of a tooth from a patient with rheumatic heart disease despite sulfadiazine therapy three days before and three days afterward. In spite of a lack of supportive evidence, the authors still believe that "the streptococcal focus in the teeth might even be etiologically significant in continuing the rheumatic activity."

Unless, as stated, the sulfonamide compounds actually do inhibit *St. viridans* in an anaerobic milieu, there seems to be little to be hoped for in the prevention of subacute bacterial endocarditis by sulfonamide therapy. Perhaps prophylaxis with antibiotics will be more successful. Both would be successful if bacteria susceptible to their action were commonly found in the blood by operative procedures. At present dental extractions and tonsillectomies should be performed only if absolutely necessary on patients with valvular disease.

A description<sup>83</sup> is given of a method, said to be reliable enough to be of clinical value in the selection of therapy, for testing the susceptibility of group A hemolytic streptococci to sulfonamide compounds.

*Sulfonamide Prophylaxis for Meningococcal Infections*—There is no longer doubt of the superiority of sulfonamide prophylaxis or therapy of meningococcal infections.<sup>4</sup> Prophylactic doses, however, cause only immediate cure or suppression of infection, the organisms soon return after treatment is stopped.<sup>84</sup> In treatment of meningitis, the response to penicillin is slower than the response to sulfadiazine, the carrier state persists, and there may be recurrences. In a report from Scotland<sup>85</sup> on over 2,000 cases, the mortality rate was reported as 17 per cent after treatment with sulfathiazole, sulfapyridine or sulfanilamide. One wonders why the reported rate is so much higher than that of many American series.

82 Clement, D. H., and Montgomery, W. R. Subacute Bacterial Endocarditis. Report of a Case with Apparent Failure of Sulfonamide Prophylaxis Complicated by Massive Hemoperitoneum, *Ann Int Med* 27:274-282 (Feb.) 1945.

83 Wilson, A. T. Method for Testing in Vitro Resistance of Group A Hemolytic Streptococci to Sulfonamides, *Proc Soc Exper Biol & Med* 58:130-133 (Feb.) 1945.

84 Phair, J. J., and Schoenbach, E. B. IV. The Transmission and Control of Meningococcal Infections, *Am J M Sc* 209:69-74 (Jan.) 1945.

85 Sulphonamides in the Treatment of Meningococcal Meningitis, Report to the Scientific Advisory Committee, Department of Health for Scotland, New York, British Information Services, 1944.

*Local Therapy with Sulfonamide Compounds*.—According to *Technical Bulletin* 147, March 1945, the War Department abandoned the local use of any chemical agent, including crystalline sulfonamide compounds, for their supposed effect in the prevention or treatment of infections. The local use of sulfonamide compounds in wounds after surgical operations, including those involving serous cavities, is not recommended. The decisions are of value in restraining the manufacture and needless waste of various sulfonamide dressings, lotions, ointments and emulsions.

#### CONTROL OF AIR-BORNE INFECTIONS

Robertson and his associates,<sup>86</sup> in a two year study of air-borne infections, show how environmental contamination by diseased persons or by carriers of pathogenic bacteria results in secondary reservoirs of infectious agents in bedding and floor dust, from which dried secretions bearing pathogenic agents are resuspended in the air in particulate form. A great increase in the numbers of air-borne streptococci follows bed making and sweeping, which probably constitute more important causes of contagion than does expulsion of "droplet nuclei" by infected persons. Measures to control such infections are designed to kill the pathogenic agents suspended in the air with bactericidal triethylene glycol vapor and by treatment of blankets, bedding, clothing and floors with oil to prevent the dispersal of dust bearing bacteria or viruses into the air.

The matter is the subject of a symposium published in the February issue of the *American Journal of the Medical Sciences*. Disinfection of air with propylene glycol and triethylene glycol causes a decrease in the incidence of infections of the respiratory tract, and in experimental studies ultraviolet rays reduced the incidence of air-borne tuberculosis in rabbits.

#### INFECTIONS OF THE RESPIRATORY TRACT

*Viral Pneumonia (Vnoid)*—It is unfortunate that common usage has permitted the term "atypical pneumonia" to be so generally applied to one of the most common of diseases.<sup>87</sup> The word "atypical" means "not typical," but the disease is certainly typical in itself. Since its first presentation as a separate entity or syndrome

86 Robertson, O. H., Hamburger, M., Loosli, C. G., Puck, T. T., and Lemm, H. M. A Study of the Nature and Control of Air-Borne Infection in Army Camps, *J A M A* 126:993-999 (Dec 16) 1944.

87 Commission on Acute Respiratory Disease. I. Atypical Pneumonia, *Am J M Sc* 209:55-58 (Jan.) 1945.

in 1938,<sup>88</sup> most evidence favored the view that one or more viruses were the cause, but, since the ultimate proof has not yet been attained in the majority of cases, many are timid about using the terms "virus" or "viral." When one judges from a comparison with known viral pneumonias, from the clinical and clinical pathologic behavior, from studies at necropsy<sup>89</sup> and from evidence that the disease can be transmitted to volunteers by inoculation with filtered secretions from patients,<sup>90</sup> what else can one believe but that agents now classified as filtrable viruses are operative?

Objection may be made even to the use of the term "pneumonia" in the name "viral pneumonia," since the same causative agent or agents give rise to far more mild attacks without pneumonia than to attacks with pneumonia. An analogy may be drawn with plague or tularemia, these infections are essentially systemic in nature although in certain cases the lungs show evidences of pneumonia, yet the terms "plague" and "tularemia" include all manifestations of either disease. It seems desirable, therefore, to employ an inclusive term, and elsewhere<sup>91</sup> I have proposed the word "viroid" to replace the meaningless name "atypical pneumonia" for the acute infections of the respiratory tract of unknown cause in question. "Viroid" has counterparts in "typhoid" and "varioid." The term means "virus-like", it includes all clinical varieties of the disease and is broad enough to allow for the possible existence of several implicated viruses. These can be named as they are eventually isolated and established as the causes of separate specific entities, as has already happened in the case of ornithosis, for example.

If the term "viroid" is tentatively used, the disease falls in line with the ones known as the

common cold, grip and influenza,<sup>92</sup> each of which may at times include attacks of specific pneumonia. An etiologic arrangement would thus appear as follows:

Epidemic Forms	Sporadic Forms
Common cold	Psittacosis, ornithosis, ailourosis
Grip	Grip
Viroid	Viroid
Influenza A, B and Y (Stuart-Harris)	Lymphogranuloma venereum
	Lymphocytic choriomeningitis
	Varicella
	Vaccinia
	Variola
	Others

The confusion in terminology is further illustrated in a paper<sup>93</sup> discussing the resemblance of occasional attacks of "atypical" pneumococcal pneumonia to "atypical pneumonia." The cases of pneumococcal pneumonia presented were of the kind which first led to the use of the word "atypical." For patients from whom no pneumococci could be isolated from the sputum, "reverse" typing was done by testing the patients' serums every other day with the capsule-swelling test using stock pneumococci of fifty-six types. The authors point out the diagnostic difficulties which may arise. In certain instances pneumococcal pneumonia may resemble viral pneumonia in many respects, but in my experience confusion does not occur often. The point to emphasize is that every effort should be made to determine the cause in all cases of pneumonia, and if evidence of the activity of certain bacteria are found the patient should be promptly treated with penicillin, sulfadiazine or specific immune serum. There is always the probability that infection with drug-sensitive bacteria may be superimposed in viral pneumonias.

**Etiologic Studies.** There is still doubt as to whether the cat pneumonia viruses of Baker and of Howard cause diseases in human beings and of the importance of the mongoose-infecting virus discovered by Horsfall. In 1 case, Howard<sup>94</sup> succeeded in causing pneumonia in cats by inoculating them with oropharyngeal washings from patients with viral pneumonia, but it was uncertain whether the causative agent came from the

88 Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111** 2377-2384 (Dec 24) 1938. Reimann, H. A., and Stokes, J. An Epidemic Infection of the Respiratory Tract in 1938-1939. A Newly Recognized Entity, *Tr. A. Am. Physicians* **54** 123-129, 1939.

89 Golden, A. Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined," *Arch. Path.* **38** 187-202 (Oct.) 1944.

90 (a) Commission on Acute Respiratory Diseases. Transmission of Primary Atypical Pneumonia to Human Volunteers, *J. A. M. A.* **127** 146-149 (Jan 20) 1945. (b) Dingle, J. H. The Present Status of the Etiology of Primary Atypical Pneumonia, *Bull. New York Acad. Med.* **21** 235-262 (May) 1945.

91 Reimann, H. A. Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? *J. A. M. A.* **127** 543 (March 3) 1945.

92 Finland, M., Parker, F., Barnes, M. W., and Joffe, L. S. Acute Myocarditis in Influenza A Infections, *Am. J. M. Sc.* **209** 455-468 (April) 1945.

93 Racker, E., Rose, S. P., and Turner, A. O. Pneumococcal Pneumonia Resembling Primary Atypical Pneumonia, *Am. J. M. Sc.* **209** 496-502 (April) 1945.

94 Howard, M. E., Blake, F. G., and Tatlock, H. Feline Pneumonia Following Inoculation with Human Nose and Throat Washings, *Federation Proc.* **4** 147-148 (March) 1945.

patients or was latent in the cats, becoming activated by the procedure. In the other case,<sup>95</sup> further studies showed that mongooses could not be infected with material from patients with viroid among Army personnel, nor could they be infected with preserved material from previously sick mongooses.

Another point as yet apparently not considered is the possibility of a genuine etiologic relation of mouse meningopneumonitis virus and mouse pneumonitis virus<sup>96</sup> found in mice to human viroid. These viruses are native in mice, and when human secretions are injected into these animals for test, the development of disease in mice, if it occurs, is usually regarded as arising from an activation of virus already present in the animals. Why can this not be an actual transmission of a disease agent which is also operative in human beings? That both human beings and mice may be subject to the same diseases is suggested by an infection with meningopneumonitis infection virus contracted by a laboratory worker and by previous studies on lymphocytic choriomeningitis. More study is needed to settle this point.

A pneumonia virus was obtained from mice inoculated with materials from the lungs of human beings with pneumonia.<sup>97</sup> The lungs of mice with this infection contained an agent which specifically agglutinated mouse erythrocytes in a manner similar to the agglutination of chicken erythrocytes with influenza virus. Fluid from the lungs of a patient with pneumonia agglutinated homologous erythrocytes and guinea pig red cells as well, but not chicken erythrocytes.

The relation of streptococcus MG, or 344, to viroid is still mysterious. In Meiklejohn and Hanford's study,<sup>98</sup> agglutinin for this coccus was present in about 40 per cent of patients, but cold agglutination occurred in a greater number and neutralizing bodies usually appeared for a virus which was isolated from these patients. Many patients in whom these neutralizing bodies developed had no streptococcus agglutinin. Further-

more, in the successful transmission experiments commented on before, streptococcus agglutinins appeared only occasionally. A relation of the streptococcus to viroid is not evident. To account for the immunologic results with the streptococcus in question, it is suggested<sup>99b</sup> that various agents involved may have antigens in common or that changes in blood proteins during the disease may give rise to nonspecific reactions.

Four papers on viral pneumonia appear in the March issue of the *Journal of Clinical Investigation*,<sup>99</sup> representing conflicting views on a number of points. The naval group of investigators<sup>100</sup> again emphasize the possible role of Streptococcus MG (Rockefeller no 344) in the pathogenesis of the disease and doubt the significance of the virus studied by the California group<sup>99a</sup> as a cause of the disease, since lesions in the lungs of animals caused by a variety of other agents were similar and none were further transmissible. The California group,<sup>99c</sup> on the other hand, report 16 cases of viral pneumonia presumably caused by their new virus, in most of which a cold agglutinin and neutralizing antibodies for the virus appeared during early convalescence. Among the volunteers of the Army investigating group<sup>99b</sup> who apparently contracted viroid by inhaling filtered secretion from patients, none showed agglutinins for Streptococcus MG, and this streptococcus was not recovered in significant numbers from any of the subjects who received either unfiltered or filtered infectious material. This evidence is said to indicate that Streptococcus MG did not play a significant role in the disease transmitted to any of the volunteers<sup>99b</sup>. In 3 of the 10 volunteers a cold agglutinin developed after the disease.

The problem is obviously complicated, and much further study is needed. Curiously, no reference is made in any of the four papers to the early contribution on the subject<sup>85</sup> in which the names of the disease now commonly used (atypical pneumonia, virus pneumonia) were

95 Dammin, G. J., and Weller, T. H. Attempts to Transmit Primary Atypical Pneumonia and Other Respiratory Tract Infections to the Mongoose, *J. Immunol.* **50** 107-114 (Feb.) 1945.

96 Eaton, M. D., and Van Herick, W. Demonstration in Cotton Rats and Rabbits of a Latent Virus Related to Pneumonia Virus of Mice, *Proc. Soc. Exper. Biol. & Med.* **57** 89-92 (Oct.) 1944.

97 Mills, K. C., and Dochez, A. R. Specific Agglutination of Murine Erythrocytes by a Pneumonitis Virus in Mice, *Proc. Soc. Exper. Biol. & Med.* **57** 140-143 (Oct.) 1944.

98 Meiklejohn, G., and Hanford, V. L. Agglutination Tests with Streptococcus No 344 in Primary Atypical Pneumonia, *Proc. Soc. Exper. Biol. & Med.* **57** 356-358 (Dec.) 1944.

99 (a) The Commission on Acute Respiratory Diseases. An Experimental Attempt to Transmit Primary Atypical Pneumonia in Human Volunteers, *J. Clin. Investigation* **24** 175-188 (March) 1945. (b) Curnen, E. C., Mirick, G. S., Ziegler, J. E., Thomas, L., and Horsfall, F. L. Studies on Primary Atypical Pneumonia. I. Clinical Features and Results of Laboratory Investigations, *ibid.* **24** 209-226 (March) 1945. (c) Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., and Horsfall, F. L. II. Observations Concerning the Relationship of a Non-Hemolytic Streptococcus to the Disease, *ibid.* **24** 227-240 (March) 1945. (d) Meiklejohn, G., Eaton, M. D., and van Herick, W. A Clinical Report on Cases of Primary Atypical Pneumonia Caused by a New Virus, *ibid.* **24** 241-250 (March) 1945.

100 The Commission on Acute Respiratory Diseases<sup>99a</sup>. Curnen<sup>99b</sup>, Thomas and others<sup>99c</sup>.

first suggested, the disease was established as a distinct entity, the first studies implicating a virus as the etiologic agent were described, a resemblance to psittacosis was pointed out, the clinical course was described (including the delayed pulmonary signs, bradycardia, nervous manifestations, roentgenographic changes, paucity of complications and ineffectiveness of sulfonamide compounds) and, finally, in which it was pointed out that the pneumonic forms may represent only the severe forms of a frequently mild epidemic infection of the respiratory tract. All of these points have been confirmed, and little of clinical importance has since been added despite the enormous amount of work done.

**Cold Agglutination** Numerous reports of studies on cold agglutination of erythrocytes during the disease have appeared. It seems that the reaction occurs in many conditions and diseases but more often and in higher titers in viroid. Titers higher than 1:160 are seldom found in other diseases but are common in severe viroid. The reactions may persist in high dilution for many months after an attack and may appear and disappear in persons without evident infection.<sup>101</sup> Yet the reaction was present in only 55 per cent of cases reported in one study,<sup>102</sup> and in only 31 per cent was the titer higher (1:64 or more) than that which occurs in other common infections. The titer is often in proportion to the severity of the disease. Cold agglutination developed in most of the experimentally infected volunteers.<sup>90</sup> In another report,<sup>103</sup> cold agglutination is said to have appeared eight to twelve days after the onset of the disease. The causative factor lay in the globulin fraction, implicating an antigen-antibody reaction. During one epidemic all patients showed a cold agglutinin, in another the reaction was not consistently present. The reaction is helpful in diagnosis only when it is strongly positive and aids in differentiating viroid from other diseases, especially from bacterial pneumonia, pulmonary tuberculosis and the psittacosis-ornithosis group of infections.

**Clinical Observations** From many clinical reports during the past year very little new information has accrued. The possibility of the development of bronchiectasis is discussed.<sup>104</sup>

but probably is not important. I have not yet encountered bronchiectasis as a sequel. The bronchial walls may be dilated, but other evidence of bronchiectasis was not present in studies made at necropsy.<sup>89</sup> In patients in which it does occur, the possibility of preexisting latent bronchiectasis must always be considered. Fractures of ribs from excessive severe coughing occurred in 19 of 500 patients in one series studied,<sup>105</sup> and so in case of excessive pain in the chest in patients with the disease this accident must not be mistaken for pleurisy, which is an uncommon accompaniment. One may question the statement in one paper<sup>106</sup> that viroid pneumonia "is not a contagious disease." In the same paper, complications of meningitis, pleural effusion and "aputid" pulmonary abscess are reported, but on poor evidence. The only indications of meningitis were a few doubtful neurologic signs and the presence of 33 lymphocytes in one sample of spinal fluid, pleural effusion and abscess were diagnosed on the basis of uncertain roentgenographic appearances alone.

**Treatment** In spite of all advice to the contrary, sulfonamide therapy is still widely employed for viroid. One author<sup>107</sup> writes that sulfonamides were actually given as a therapeutic diagnostic test. Certainly better methods of diagnosis are in order. Penicillin, likewise shown to be ineffective against viral infections,<sup>81</sup> is said to give good results,<sup>108</sup> but the report is unconvincing, no controls were observed.

**Varying Forms of Viral Pneumonia** Two fatal cases of influenza associated with bacteria-free pneumonia are described.<sup>92</sup> Influenza virus A was obtained from the pneumonic areas at necropsy, giving further proof that a viral form of pneumonia occurs in true influenza.

A small outbreak of a severe form of a psittacosis-like disease, with 8 deaths in 19 known cases, occurred in Louisiana.<sup>109</sup> The disease can

105 Harvey, R. M. Rib Fractures in Atypical Pneumonia, *Am J Roentgenol* **52**: 487-493 (Nov) 1944.

106 Glendy, R. E., Beaser, S. B., and Hankins, W. D. Primary Atypical Pneumonia of Unknown Cause, with Unusual Manifestations and Complications, *Arch Int Med* **75**: 30-38 (Jan) 1945.

107 Gunderson, S. Primary Atypical Pneumonia of Unknown Etiology, *New England J Med* **231**: 697-700 (Nov 23) 1944.

108 Short, J. J. Penicillin in the Treatment of Primary Atypical Pneumonia, *U S Nav M Bull* **43**: 974-980 (Nov) 1944.

109 Olson, B. J., and Treuting, W. L. An Epidemic of a Severe Pneumonitis in the Bayou Region of Louisiana. I. Epidemiological Study, *Pub Health Rep* **59**: 1299-1311 (Oct 6) 1944. Treuting, W. L., and Olson, B. J. II. Clinical Features, *ibid* **59**: 1331-1356 (Oct 13) 1944. Binford, C. H. and Hauser, G. H.

101 Favour, C. B. Autohemagglutinins—"Cold Agglutinins," *J Clin Investigation* **23**: 891-897 (Nov) 1944.

102 Commission on Acute Respiratory Diseases. Cold Hemagglutinins in Primary Atypical Pneumonia and Other Respiratory Infections, *Am J M Sc* **208**: 742-750 (Dec) 1944.

103 McNeil, C. The Relationship of Cold Agglutinins to the Cause of Primary Atypical Pneumonia, *Am J M Sc* **209**: 48-54 (Jan) 1945.

104 Kay, E. B. Bronchiectasis Following Atypical Pneumonia, *Arch Int Med* **75**: 89-104 (Feb) 1945.

probably be included with the sporadic forms of viral pneumonia, since no mild forms of it were recognized. It was thought to have been spread from person to person as an air-borne infection, but the source of the disease is unknown. A virus was readily isolated by the intraperitoneal or intranasal inoculation of mice with washings from the throats and with material from the lungs of patients studied at necropsy. It appeared to belong to the psittacosis group of pathogens. One of my own patients with a severe attack of psittacosis or ornithosis had shot quail in South Carolina ten days before the onset of illness. This occurrence suggests the possible existence of ornithosis in game birds.

Report<sup>110</sup> was made of diagnosis of 6 cases of ornithosis on the inadequate basis of a single positive complement fixation reaction in each instance and of possible contact with pigeons. Diagnosis can be accepted tentatively only if the tests show a rise of titer and then a fall after the disease and if there was reasonable proof of contact with infected birds, positive diagnosis can be made only if the agent is isolated and identified. Reports like this one confuse the issue and should not be published.

Pinkerton and his co-workers<sup>111</sup> report a subacute or chronic form of pneumonia in infants, characterized by large multinucleated cells and cytoplasmic and intracellular inclusions in the pulmonary tissues. The histologic reactions resemble those seen occasionally in measles and in canine distemper and are different from those in the pneumonia of infants described by Goodpasture and by Adams. The studies suggest the need for investigating the possibility that human viral pneumonia can be contracted from dogs with distemper.

*Other Forms of Pneumonia*—Interest is increasing in transitory pulmonary infiltrations associated with eosinophilia, often called Loeffler's syndrome<sup>112</sup>. It would seem that the condition may occur as a result of allergic sensitization to the products of many parasites, including ascaris, liver fluke and *Endamoeba histolytica*. Perhaps any prolonged mild infection associated with allergic phenomena may cause the syndrome.

III Pathological Observations, *ibid* 59 1363-1373 (Oct 13) 1944. Olson, B. J., and Larson, C. L. IV A Preliminary Note on Etiology, *ibid* 59 1373-1374 (Oct 20) 1944.

110 Levinson, D. C., Gibbs, J., and Beardwood, J. T. Ornithosis a Cause of Sporadic Atypical Pneumonia, *J. A. M. A.* 126 1079-1084 (Dec 23) 1944.

111 Pinkerton, H., Smiley, W. L., and Anderson, W. A. D. Giant Cell Pneumonia with Inclusions, *Am. J. Path.* 21 1-15 (Jan) 1945.

112 Transitory Pulmonary Infiltration Associated with Eosinophilia—Loeffler's Syndrome, editorial, *J. A. M. A.* 126 837 (Nov 25) 1944.

*Pneumonia in Association with Malaria*—When pneumonia occurs with malaria, it is often difficult to decide whether it is of bacterial or viral origin or is a manifestation of malaria itself. Most observers do not believe that a specific malarial pneumonia occurs but believe that the pulmonary disturbance is caused by blockage of vessels with disintegrated red cells by atelectasis or by other factors. In one series of patients,<sup>113</sup> pneumonia was diagnosed for 37 per cent. The symptoms resembled those of viral pneumonia. British clinicians regard the relation of viral pneumonia to malaria as fortuitous.<sup>114</sup>

Wood and Pierson<sup>115</sup> studied 1 of the rare cases, or at least 1 of the rarely recognized cases of pulmonary adenomatosis. The lesion in the lung was a diffuse alveolar epithelial hyperplasia resembling noncaseating disseminated miliary tuberculosis and also resembling the disease called epizootic adenomatosis, or *jaagsiekte*, occurring in sheep and other animals. Their observations raise a number of important questions: (1) whether the disease in human beings is related to that in sheep, (2) whether a virus may be the cause, giving rise to a tumor-like hyperplasia like that caused by Shope's papilloma virus, (3) whether the cells lining the alveoli are epithelial in nature, and (4) whether there is a possibility that the disease is not so rare as is believed and may be mistakenly diagnosed as pulmonary cancer.

*Influenza*—Shope<sup>116</sup> reviews the developments in the knowledge of influenza. He reiterates his own theory that human influenza was transmitted to hogs during the pandemic of 1918. The virus of hog influenza, if it was related to that outbreak, as it seems to have been, is the only proof of the identity of the disease with influenza as it is now understood. One wonders, however, if hogs have been infected only since 1918, as Shope suggests. They certainly must have been exposed to the pandemic of 1889 and to previous ones and like human beings, perhaps served as occasional reservoirs of infection. Both would seem to be able to serve as mutual

113 Applebaum, I. L., and Shrager, J. Pneumonitis Associated with Malaria, *Arch. Int. Med.* 74 155-162 (Sept) 1944.

114 Fleming, J., Lindeck, E. W., and Evans, I. H. "Primary Atypical Pneumonia" An Epidemic Associated with Malaria, *Brit. M. J.* 1 689-693 (May 19) 1945.

115 Wood, D. A., and Pierson, P. H. Pulmonary Alveolar Adenomatosis in Man. Is This the Same Disease as Jaagsiekte in Sheep? *Am. Rev. Tuberc.* 51 205-224 (March) 1945.

116 Shope, R. E. Old, Intermediate and Contemporary Contributions to Our Knowledge of Pandemic Influenza, *Medicine* 23 415-455 (Dec) 1944.

transmitters, to begin or to propagate epidemics in either or both species

British views on influenza are summarized by Stuart-Harris<sup>117</sup>. In many epidemics in England during the past few years various combinations of influenza A, B and unknown forms occurred. In one epidemic 50 per cent of attacks were of unknown cause but were called influenza Y. There are three theories to account for this Y type of infection: (a) It is caused by one or more as yet unknown viruses, (b) it is caused by the basic virus of influenza, devoid of antigenic ability, and (c) it is caused by either type A or type B virus, which for some unknown reason cannot be isolated and gives rise to no serologic response.

Epidemics are unpredictable, as is shown by the author's mistake in predicting a large outbreak. In spite of the prevalence of influenza virus A in 1941, the vast disorganization caused by aerial bombing was not accompanied with an anticipated epidemic. In fact, influenza is the only important epidemic disease unaffected thus far by the war<sup>118</sup>.

Acute collapse of the circulatory system and a shocklike state have long been recognized as serious complications or sequelae of influenza and of viral pneumonia. They were thought to be caused by some toxic effect on the central nervous system or on the heart itself. Finland and his associates<sup>92</sup> review the information on the subject and describe 2 cases of their own. Both patients had influenza, and at necropsy bacteria-free pneumonitis and acute myocarditis were found. Influenza virus A was thought to have caused the myocardial lesions.

**Prevention of Influenza**—In discussing the prospects of preventing epidemics of influenza, one author believes in the use of all procedures available, including general measures of hygiene, aerial disinfection, quarantine and vaccine. If a virus of different characteristics from that against which vaccines are available were operative, vaccine would not help unless the current virus were used as an antigen.

Attempts to improve influenza vaccine are being made<sup>119</sup>. The use of Hirst's concentrated vaccine reduces the attack rate but not enough to be of practical value. Vaccine, if it is used at all, is best given early in an outbreak after its identification, if given in anticipation of an out-

break it may be wasted, since outbreaks of influenza are unpredictable and immunity is of brief duration. Stanley<sup>120</sup> describes a successful procedure of centrifugation for the production of concentrated vaccine in large amounts. Other studies show that the immunizing effect on mice of formaldehyde-treated influenza virus can be enhanced and prolonged by precipitation of the virus on calcium phosphate<sup>121</sup>.

The intraperitoneal injection of atropine sulfate before the intranasal inoculation of influenza virus in mice decreases the incidence and extent of infection of these animals<sup>122</sup>.

**Other Studies on Influenza** According to Hirst,<sup>123</sup> the most sensitive method to recover influenza virus is through the inoculation of chick embryos by the allantoic route with throat washings containing penicillin to suppress bacterial growth. Eaton and his associates,<sup>124</sup> however, found the chick embryo technic to be quicker but less reliable than the technic of inoculation of either hamsters or ferrets. Others,<sup>125</sup> using the chick embryo method, record the important finding of influenza virus in the throats of 5 of 13 healthy persons who had been in contact with patients suffering from influenza A. In 9 of the 13 studied, significant increase of antibodies to influenza virus A appeared according to the test of inhibition of agglutination of red blood cells. In 3 of those from whom the virus was isolated, no antibodies developed. The results verify an old concept that some healthy persons carry the virus and may be of great importance in the spread of influenza.

The question arises<sup>126</sup> as to whether influenza virus causes neurologic disturbances by actually

120 Stanley, W. M. The Preparation and Properties of Influenza Virus Vaccines Concentrated and Purified by Differential Centrifugation, *J. Exper. Med.* **81**: 193-217 (Feb.) 1945.

121 Salk, J. E. The Immunizing Effect of Calcium Phosphate Adsorbed Influenza Virus, *Science* **101**: 122-124 (Feb. 2) 1945. Stanley, W. M. The Precipitation of Purified Concentrated Influenza Virus and Vaccine on Calcium Phosphate, *ibid.* **101**: 332-335 (March 30) 1945.

122 Wheeler, A. H., and Nungester, W. J. The Effect of Atropine Sulfate on the Course of Influenza Virus Infection, *Science* **100**: 523-524 (Dec. 8) 1944.

123 Hirst, G. K. Direct Isolation of Influenza Virus in Chick Embryos, *Proc. Soc. Exper. Biol. & Med.* **58**: 155-157 (Jan.) 1945.

124 Eaton, M. D., Corey, M., van Herick, W., and Meiklejohn, G. A Comparison of Various Methods of Demonstrating Influenza Virus in Throat Washings, *Proc. Soc. Exper. Biol. & Med.* **58**: 6-9 (Jan.) 1945.

125 Crowley, J. H., Thigpen, M. P., and Rickard, E. R. Isolation of Influenza A Virus from Normal Human Contacts During an Epidemic of Influenza A, *Proc. Soc. Exper. Biol. & Med.* **58**: 345-356 (Dec.) 1944.

126 Henle, G., and Henle, W. Neurological Signs in Mice Following Intracerebral Inoculation of Influenza Viruses, *Science* **100**: 410-411 (Nov. 3) 1944.

117 Stuart-Harris, C. H. Influenza and the Influenza Viruses, *Brit. M. J.* **1**: 207-216 (Feb. 17), 251-257 (Feb. 24) 1945.

118 Stowman, K. The Epidemic Outlook in Europe, *J. A. M. A.* **128**: 185-188 (May 19) 1945.

119 Hirst, G. K., Rickard, E. R., and Friedewald, W. F. Studies in Human Immunization Against Influenza. Duration of Immunization Induced by Inactive Virus, *J. Exper. Med.* **80**: 265-273 (Oct.) 1944.

growing in brain tissue or by its toxicity in a manner similar to that of the psittacosis group of pathogens, as reported by Rake and Jones last year

One author,<sup>127</sup> impressed by certain reports of reduction of the incidence of colds by sulfonamide prophylaxis, argues that colds therefore are not caused by viruses. Without evidence for his assumption, he writes that most colds are caused by streptococci, that is, the *Str. viridans* dissociates into pathogenic hemolytic streptococci. Such transformation is not known to occur. Other vacuous arguments are also presented, but his views are contrary to general opinion.

*Pneumococcic Pneumonia*—Speransky, a Russian, basing his idea on the reaction in rabbits' lungs after intracranial trauma, believes that human pneumonia results from stimuli originating in the central nervous system.<sup>128</sup> This theory is cited as a reason for the sudden beginning of lobar pneumonia. Because sulfonamide therapy gave unfavorable results, he recommends the subcutaneous injection of procaine hydrochloride solution into the area of the rhomboid muscles for "its neurotrophic effect." Within eighteen to twenty-four hours after injection, recovery is said to occur. The line of reasoning is suggestive of osteopathic theories. The author makes no mention of studies on the pathogenesis of pneumonia by American or other scientists. However, regardless of Speransky's logic, others<sup>129</sup> have also felt that nervous influence may play an important role in lobar pneumonia in accounting for both its sudden onset and its sudden ending, but in a different manner.

Ginsburg,<sup>130</sup> adopting Speransky's suggestion, reports good results in treating thyrotoxicosis, nephritis, pneumonia and other diseases with his method. From his 49 cases of pneumonia, some of the charts look impressive, recovery occurred twelve to forty-eight hours after the injection of procaine hydrochloride, but the data given are so meager as to render critical judgment difficult, only 1 death occurred. No laboratory studies except leukocyte counts were made, because of war conditions. The work needs confirmation, to say the least.

*Diphtheria*—Diphtheria is the leading epidemic disease in war-torn Europe.<sup>131</sup> More than 1,000,000 cases occurred in 1943. The most serious development is not so much the spread of the disease as its change in type, increased severity and resistance to antitoxic treatment. In Germany<sup>131a</sup> one third of the population of a large city were considered to be carriers. Healthy carriers are responsible for almost all cases. In Baltimore,<sup>132</sup> fortunately, the gravis type of diphtheria has not been more prevalent than heretofore.

*Coccidioidomycosis*—This infection continues to be of importance, especially among military personnel stationed in western areas where the disease is endemic.<sup>133</sup> In certain camps cutaneous reactions to the specific antigen developed in 80 per cent of the inhabitants after exposure to infection. In the great majority of instances the infection is so mild as to be unrecognized, in certain patients the symptoms are those of a mild infection of the respiratory tract and in others of pulmonary tuberculosis. In rare cases the chronic or severe granulomatous stage develops. The advanced forms seem to be much more likely to develop in Negroes. Basal meningitis occasionally occurs in coccidioidomycosis. A case is described<sup>134</sup> in which the outstanding lesions of the disease were in the brain.

Men exposed to infection in an area where the disease is endemic may go elsewhere, and the disease may develop in places where it would not be thought of or diagnosed unless special diagnostic tests were made. There is no satisfactory treatment.

*Histoplasmosis*—Palmer<sup>135</sup> made a survey in order to learn the cause of pulmonary calcification not related to tuberculosis or to coccidioidomycosis. In a study of 3,000 persons, of whom 294 had pulmonary calcification, 23 per cent had a positive reaction to histoplasmin, a filtrate of broth culture of *Histoplasma capsulatum*. Great

131 (a) Kollath, W. Problems of Diphtheria, *Deutsche med. Wchnschr.* **70** 203-204 (April) 1944.  
(b) Stowman.<sup>118</sup>

132 Frobisher, M., Adams, M. L., and Kuhns, W. J. Characteristics of Diphtheria Bacilli Found in Baltimore Since November 1942, *Proc. Soc. Exper. Biol. & Med.* **58** 330-334 (April) 1945.

133 Lee, R. V. Coccidioidomycosis in Western Flying Training Command, California & West Med **61** 133-134 (Sept.) 1944. Denenholz, E. J., and Cheney, G. Diagnosis and Treatment of Chronic Coccidioidomycosis, *Arch. Int. Med.* **74** 311-330 (Nov.) 1944.

134 Schlumberger, H. G. A Fatal Case of Cerebral Coccidioidomycosis with Cultural Studies, *Am. J. M. Sc.* **209** 483-496 (April) 1945.

135 Palmer, C. E. Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, *Pub. Health Rep.* **60** 513-520 (May 11) 1945.

127 Brown, E. E. Common Cold Not Caused by Virus, *Northwest Med.* **44** 39-41 (Feb.) 1945.

128 Speransky, A. D. Experimental and Clinical Lobar Pneumonia, *Am. Rev. Soviet Med.* **2** 22-27 (Oct.) 1944.

129 Reimann, H. A. The Pneumonias, Philadelphia, W. B. Saunders Company, 1938, p. 183.

130 Ginsburg, E. M. Pathogenesis and Treatment of Lobar Pneumonia, *Am. Rev. Soviet Med.* **2** 28-36 (Oct.) 1944.

differences in the percentage of reactions were noted between those from Minnesota (6 per cent) and from Missouri (66 per cent). These results suggest that histoplasmosis is endemic in certain regions and may be a frequent cause of pulmonary calcification and that the disease may be far more common in mild form than it is believed to be. Parsons and Zarafonetis<sup>136</sup> review 71 cases of histoplasmosis and the subject in general. The infection is apparently worldwide in distribution, and cases are being recognized with increasing frequency. (The infection is not spreading.) The symptoms and signs often resemble those of many other diseases, and correct diagnosis may not be made unless biopsy, culture and other types of examinations are done. There is no specific treatment for the disease. It is reported that most cases end fatally. This observation is probably wrong in view of those made by Palmer<sup>135</sup>. The severest and fatal cases are most apt to be diagnosed, mild ones may escape notice and diagnosis.

Another spontaneous case of histoplasmosis in a dog is reported<sup>137</sup>. A disease thought to be histoplasmosis in a cat on further study was diagnosed as toxoplasmosis<sup>138</sup>. In about 3 per cent of adults in St. Louis, evidence of previous infection was present in the serum<sup>139</sup>.

*Pulmonary Tuberculosis*—In the light of certain studies on coccidioidomycosis and histoplasmosis just mentioned, doubt may be cast on observations<sup>140</sup> reported from San Antonio, Texas, which is said to have the highest tuberculosis rate in this country but which is in a region where coccidioidomycosis is endemic. In this study, diagnosis of tuberculosis was made for about 5 per cent of 20,000 residents on the basis of a roentgenographic survey alone. Obviously there is need of reinvestigation of the data. In Los Angeles, for example, the incidence of positive coccidioidin cutaneous reactions in one group

studied was 26 per cent<sup>141</sup>. At necropsy several patients who had given a positive reaction all revealed healed calcified lesions indistinguishable from those of tuberculosis. Another disease which may at times easily be mistaken for pulmonary tuberculosis is paragonimiasis,<sup>142</sup> which may be encountered especially among returned war veterans. In this disease, chronic cough, pain in the chest and bloody sputum are common.

None of the sulfonamide drugs now available has given any clinical therapeutic effect sufficiently encouraging to warrant its use in the treatment of tuberculosis<sup>143</sup>. The same may be said at present for various antibiotics thus far tested.

*Experimentally Produced Diseases of the Respiratory Tract*—In extensive studies, Melville and Stehle<sup>144</sup> tested the effect of seventy-nine chemical compounds, including sixty-one aminobenzene derivatives, on experimental tuberculosis in guinea pigs. None of the agents tested showed any evidence of curative action, since in all experiments gross evidence of tuberculosis could still be detected in all treated and untreated animals no matter how long they survived.

An attack of pneumonic plague contracted during laboratory research is reported<sup>145</sup>. The patient recovered after a stormy course, during which he received sulfadiazine and penicillin, but it is uncertain that recovery can be ascribed to either. No secondary or contact attacks occurred among associates or attendants. The patient had received antiplague vaccine one year before, but six months later his serum contained no demonstrable protective bodies. Plague pneumonia is generally believed to be uniformly fatal, but it is safe to guess that numerous undiagnosed cases end in recovery. It would be of great interest to test the effects of streptomycin in plague.

141 Butt, E. M., and Hoffman, A. M. Healed or Arrested Pulmonary Coccidioidomycosis. Correlation of Coccidioidin Test with Autopsy Findings, *Am J Path* **21** 485-506 (May) 1945.

142 Miller, J. J., and Wilbur, D. L. Paragonimiasis (Endemic Hemoptysis), *U S Nav M Bull* **42** 108-110 (Jan) 1944.

143 Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. Present Status of Chemotherapy in Tuberculosis, *Ann Int Med* **22** 696-703 (May) 1945.

144 Melville, K. I., and Stehle, R. L. Chemotherapy in Experimental Tuberculosis, *Canad J Research* **22** 95-121 (Dec) 1944.

145 Minter, E. J. Pneumonic Plague. Report of a Case with Recovery, *J A M A* **128** 281-283 (May 26) 1945.

136 Parsons, R. J., and Zarafonetis, C. J. D. Histoplasmosis in Man. Report of Seven Cases and a Review of Seventy-One Cases, *Arch Int Med* **75** 1-23 (Jan) 1945.

137 Callahan, W. P. Spontaneous Histoplasmosis Occurring in a Dog, *Am J Trop Med* **24** 363-366 (Nov) 1944.

138 Meleney, H. D. Toxoplasmosis Mistaken for Histoplasmosis in a Cat, *Am J Trop Med* **25** 163 (March) 1945.

139 Callahan, W. P. Incidence of Toxoplasmic Infections in the St. Louis Area, *Proc Soc Exper Biol & Med* **59** 68-70 (May) 1945.

140 Gould, D. M. Mass X-Ray Survey in San Antonio, *Pub Health Rep* **60** 117-126 (Feb 2) 1945.

(To Be Concluded)

## Book Reviews

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**Essentials of Allergy** By Leo H. Crip, M.D.  
Price, \$5 Pp 381, with 42 illustrations and 1 plate  
in color Philadelphia J. B. Lippincott Company,  
1945

As its title implies, this small book deals with the important aspects of allergy. Packed into the volume are chapters on the immunology of allergy, anaphylaxis and serum sickness, diagnosis and treatment of allergy in general and of each allergic disease, with special emphasis on bronchial asthma, hay fever and allergy of the skin. Other allergic conditions are also considered. Because of limitation of space, the outline form of discussion is used. The book is exceedingly well written and full of clear and concise information of special interest for medical students and general practitioners, and even for allergists. Reports of cases illustrate teaching points. The section on bronchial asthma and its relation to the heart is especially good, as is also that on psychosomatic aspects in treatment.

A few minor corrections should be noted. The author might well have been more emphatic in stating that true migraine is almost always due to food allergy and should therefore be investigated from the viewpoint of allergy. He states that "roentgen ray therapy has not proved its value in the treatment of bronchial asthma." Many workers have shown that this method does give good, though only temporary, results. His suggestion that 50 per cent sucrose should be injected intravenously in status asthmaticus should not be followed, it is known that such treatment usually harms the kidneys. He states that "there is no eosinophilia" in patients with intrinsic asthma, that is, asthma with negative cutaneous reactions. Most investigators have found only a little difference between the percentage of eosinophils in persons with extrinsic and with intrinsic asthma. Also, most men who have experience with both the scratch and the intradermal method of skin testing will not agree with his opinion that intradermal testing is "less painful" than the scratch method. With these minor exceptions, the book is excellent throughout and should be widely used. As the author states, larger volumes on the subjects should also be consulted.

**Clinical Case-Taking** By George R. Herrmann, M.D.  
Third edition Price, \$1.75 Pp 192 St. Louis  
The C. V. Mosby Company, 1945

This is a manual of procedure for ward and bedside practice. Several pages are devoted to the plan, scope, objectives, principles, art and technic of case taking, and these are followed by several chapters of detailed directions for history taking and for physical examination. More than half of the volume is composed of chapters on semiology of diseases and systems. Apparently the purpose of these chapters is to familiarize the

student with terminology and to point out the common symptoms and findings of some diseases. The book should be of value to the beginner in physical diagnosis.

**Duodenal and Jejunal Peptic Ulcer** By Rudolf Nissen, M.D. Price, \$4.75 Pp 143, with 123 illustrations New York Grune & Stratton, Inc., 1945

The reviewer has little to add to the comments of Wangenstein in his foreword to this little book. While he deals largely with the technic of various operations, the author also presents with reasonable logic his rationale for one or another procedure. None the less it is clear that the whole subject of operation for duodenal ulcer remains a complex one, and the exact reasons for relief and failure are often difficult to evaluate and must be involved with the psychologic aspects of the situation. There are many excellent illustrations and a bibliography.

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## News and Comment

### 1945 MEETING OF THE MISSISSIPPI VALLEY MEDICAL SOCIETY CANCELED

The 1945 meeting of the Mississippi Valley Medical Society, which was to be held in St. Louis in September, has been canceled because of war restrictions. Plans are being made to hold the 1946 meeting at the Jefferson Hotel in St. Louis September 25 through 27.

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## Correspondence

### PERNICIOUS ANEMIA IN CHINESE

*To the Editor*—Dr. Chester S. Keefer was good enough to call to my attention an error which Dr. Rappolt and I had made in citing Dr. Yang and himself in our article in the June 1945 issue of the *Archives* (p. 404). In this article we said "Yang and Keefer have reported the only 2 cases of pernicious anemia in Chinese observed previously on this continent. They were cases of Minot's and apparently were typical." Yang and Keefer have reported 2 cases of pernicious anemia in Chinese patients, but these were observed in Peiping, China. In their article they refer to a case which Minot had observed in the United States. This case was not observed by them and has not been reported by Minot.

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## ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

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NEW HAVEN, CONN

MINNEAPOLIS

Rheumatic fever is the cause of much disability and of many deaths resulting from the acute process and from the chronic heart disease which so frequently follows. The investigation of preventive and therapeutic measures for the control of this serious disease has been greatly hampered by the failure of many studies to establish satisfactorily its etiology and pathogenesis.

During the past twenty years it has become increasingly apparent that infection by hemolytic streptococci is in some way related to the development of the rheumatic state. The evidence on which this fact has been based has been of an indirect nature and may be summarized as follows: 1. Rheumatic fever has been observed to follow known hemolytic streptococcus infections, particularly of the respiratory tract. In these circumstances it has been noted that the initial acute illness is usually followed by a latent or quiescent period, which terminates in the more or less explosive appearance of arthritis or carditis.<sup>1</sup> 2. Epidemics of rheumatic fever often follow outbreaks of scarlet fever or streptococcal sore throat.<sup>2</sup> 3. Recrudescences of activity frequently appear when infection by hemolytic streptococci occurs in persons who have previously undergone attacks of rheumatic fever.<sup>3</sup> 4. Immunologic investigations have indicated

that high titers of various antistreptococcus antibodies and cutaneous hypersensitivity to products and fractions of hemolytic streptococci are usually demonstrable in persons suffering from acute rheumatic fever or from recurrences of this disease.<sup>4</sup>

A further approach to the problem lay in the detailed study of large groups of persons in whom hemolytic streptococcus infections of the respiratory tract had occurred, for the purpose of determining the natural history of such infections and their relationship to the rheumatic state. This approach has rarely been possible in civilian practice, because prolonged and intimate follow-up of the infected group is necessary. It became clear, with the onset of the present war and the rapid mobilization of large numbers of troops, that in certain areas hemolytic streptococcus disease of the respiratory tract and rheumatic fever

3 (a) Coburn, A. F. The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931. (b) Collis, W. R. F. Acute Rheumatism and Haemolytic Streptococci, *Lancet* **1** 1341, 1931. Jones, T. D., and Mote, J. R. The Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, *J. A. M. A.* **113** 898 (Sept 2) 1939.

4 Todd, E. W. Antihemolysin Titers in Hemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, *Brit. J. Exper. Path.* **13** 248, 1932. Coburn, A. F., and Pauli, R. H. Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, *J. Exper. Med.* **56** 651, 1932. Boisvert, P. J. The Streptococcal Antifibrinolysin Test in Clinical Use, *J. Clin. Investigation* **19** 65, 1940. Mote, J. R., and Jones, T. D. Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever and Rheumatoid Arthritis, *J. Immunol.* **41** 35, 61 and 87, 1941. Swift, H. F., and Cohn, A. E. Type Specific Anti-M Precipitins in Rheumatic and Non-Rheumatic Patients with Hemolytic Streptococcal Infections, *Proc. Soc. Exper. Biol. & Med.* **34** 849, 1936. Collis, W. R. F., Sheldon, W., and Grayhill, N. Cutaneous Reactions in Acute Rheumatism, *Quart. J. Med.* **1** 511, 1932. Gibson, H. J., Thomson, W. A. R., and Stewart, D. The Haemolytic Streptococcus as a Factor in the Causation of Acute Rheumatism, *Arch. Dis. Childhood* **8** 57, 1933. Taran, L. M., Jablon, I. M., and Weyr, H. N. Immunologic Studies in Rheumatic Fever. I. Cutaneous Response to Type-Specific Proteins of the Hemolytic Streptococcus, *J. Immunol.* **49** 209, 1944. Coburn<sup>3a</sup>

Colonel T. E. Harwood Jr., Major James Blanton and Captain Howard Coggeshall cooperated and assisted in this work.

The laboratories of the Department of Medicine, Stanford University School of Medicine, were made available to the Commission on Hemolytic Streptococcal Infections for certain studies.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1 (a) Escherich, T., and Schick, B. Scharlach, Vienna, A. Holder, 1912. (b) Schlesinger, B. The Relationship of Throat Infection to Acute Rheumatism in Childhood, *Arch. Dis. Childhood* **5** 411, 1930.

2 Paul, J. R. and others. The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, New York, Metropolitan Life Insurance Company for the American Heart Association, 1943.

were prevalent. A program was therefore established in an army camp in such an area, with the assurance that a large number of infected persons would be available for study. The homogeneity of the group as to age, sex and degree of exposure to infectious agents and their availability for prolonged follow-up suggested that useful information would be obtained. In addition, various immunologic methods had been perfected for the study of antibody response<sup>4</sup> in infected persons and for the accurate subdivision of the hemolytic streptococci into groups and, of greatest importance, into types.<sup>5</sup> These techniques permitted more precise study of disease caused by these organisms than had hitherto been possible.

This paper is a summary of the bacteriologic and clinical results of this work so far as it bears on the pathogenesis of rheumatic fever. Much information was obtained in regard to the bacteriology, immunology, nature and treatment of the acute initial phase of hemolytic streptococcus sore throat and of complications following this streptococcic condition, which will be presented elsewhere.

#### PLAN OF STUDY

All patients suffering from disease of the respiratory tract of any type were admitted to certain wards in the station hospital, where they were seen by one of us. A history was obtained, a physical examination performed, cultures of materials from the throat and nose made and a Dick test done. Patients discovered, on clinical and bacteriologic grounds, to be suffering from infection by hemolytic streptococci were transferred to special wards, where a permanent trained nursing staff was maintained, which permitted the execution of therapeutic and other investigative programs. These patients were studied by means of a variety of laboratory procedures. Cultures were made repeatedly from materials from the nose and throat, and the isolated hemolytic streptococci were classified serologically by the precipitin technique of Lancefield.<sup>5</sup> Serial white blood cell counts, erythrocyte sedimentation rates (Westergren) and electrocardiograms were obtained. Each patient was studied for not less than three weeks and frequently for a longer period.

#### RESULTS

During the period of intensive study, from Jan 1 to April 15, 1944 approximately 1,500 patients came under observation. Group A hemolytic streptococci were not isolated from the throats of 871 patients, whose disease processes may definitely be regarded as nonstreptococcic in origin. Four hundred and ten were considered to be infected by group A streptococci, because large numbers of these organisms were

recovered from the nasopharynx and because the physical examinations revealed some combination of the following signs: (1) tonsillar exudate, (2) edema and redness of the pharyngeal tissues and (3) adenitis of the anterior cervical lymph nodes, with tenderness.<sup>51</sup> Three hundred persons suffered from illnesses somewhat more difficult to classify. Many of these were patients with clinically typical virus infections who were nasopharyngeal carriers of hemolytic streptococci. There were also many cases of pneumococcal pneumonia and of the ordinary communicable diseases.

Rheumatic fever never followed any of the 1,100 infections definitely or probably not of streptococcic origin. It did appear in 15 of the 410 men with infections due to group A hemolytic streptococci.

It is, therefore, clear that infection by hemolytic streptococci always preceded the development of rheumatic fever in this group. Further information as to the nature and pathogenesis of this disease was obtained by the detailed study of a large number of cases of hemolytic streptococcus sore throat and of scarlet fever. The intensive program just described was carried out in 296 cases of these diseases, serial electrocardiograms being obtained in 185. Very early in the course of this investigation it became apparent not only that typical rheumatic fever was occurring occasionally in some men of this group, but that many others were failing to return to a full state of health after the acute phase of the initial streptococcic disease. In some, the continuing activity of the disease process was caused by local suppuration such as sinusitis and otitis media. In many, however, no evidence of such complications could be discovered. Electrocardiographic evidence of carditis was discovered in certain of these cases. It is, therefore, desirable to describe the natural history of acute streptococcic sore throat as it was observed during this study, with special reference to the period after the initial suppurative phase of the disease had subsided. Patients with and without rash are included together for the purpose of this analysis.

#### THE POSTSTREPTOCOCCIC STATE

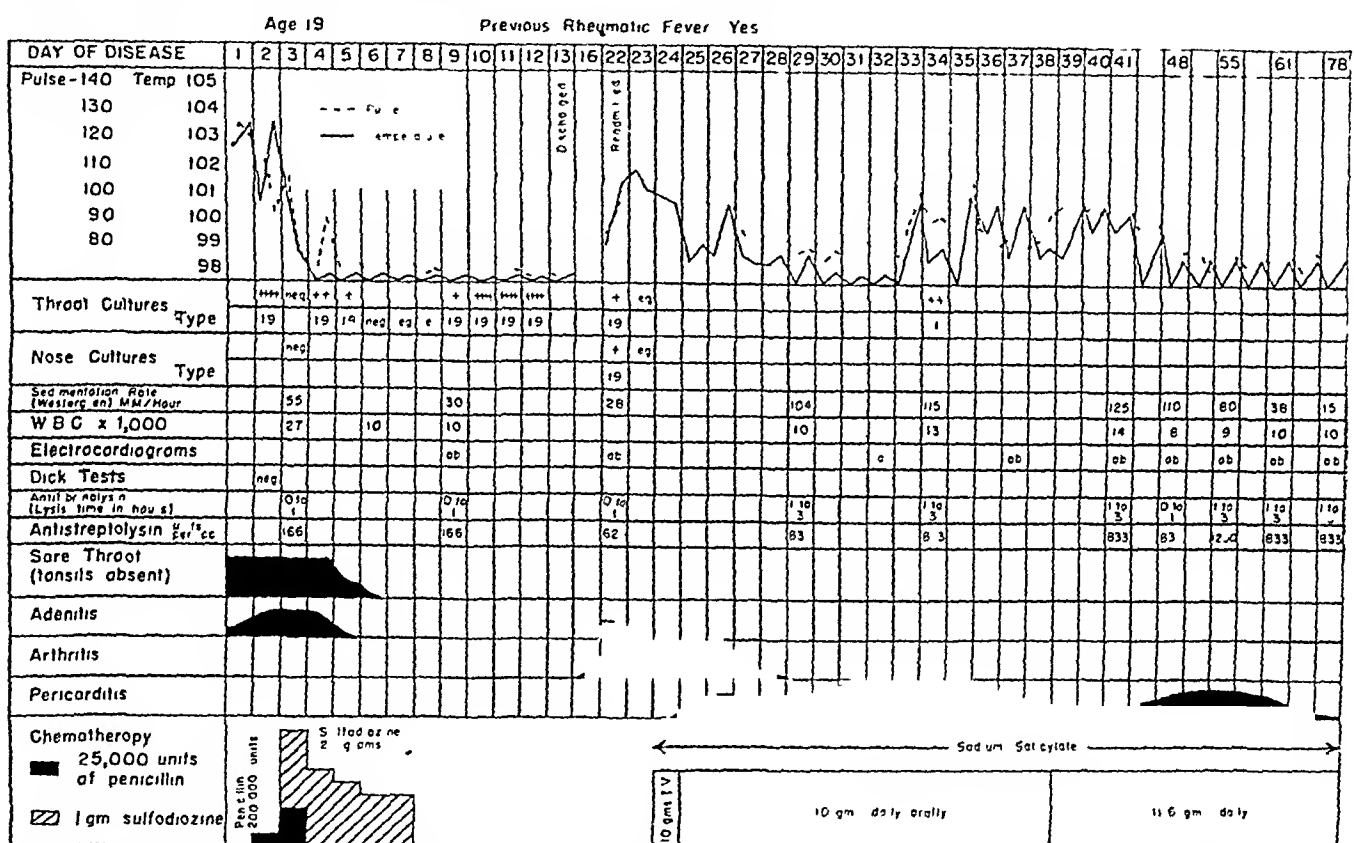
*Rheumatic Fever*.—Rheumatic fever, characterized by migrating polyarthritis, fever, rapid erythrocyte sedimentation rate and, in 8 cases, electrocardiographic evidence compatible with the presence of carditis, developed in 15 of the

<sup>5</sup> Lancefield, R. C. Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941.

<sup>5a</sup> A significant antistreptolysin and/or antifibrinolysin response occurred in 87.5 per cent of 342 of these patients, for whom suitable serial determinations were made, indicating that the clinical diagnosis was usually correct.

sore throat, in which the erythrocyte sedimentation rate has returned to normal within two to three weeks. Several of these men also failed to make a complete clinical recovery, in that easy fatigability persisted after the acute illness of the respiratory tract had subsided.

Also of considerable interest was the discovery of electrocardiographic evidence of carditis several days to weeks before the development of arthritis. Abnormal electrocardiograms were obtained on the ninth, thirty-sixth and twenty-third days after the onset of the acute sore throat in 3 cases, but arthritis was not observed until five, nineteen and fifty-two days later. These facts can be emphasized by the presentation of a case record.



*Absence of Latent Period*—Previous studies have indicated that rheumatic fever does not immediately follow an acute streptococcic disease of the respiratory tract but is separated from it by a latent, or quiescent, period of one to two weeks in duration, and it has been implied that during this interval the patients are clinically well. Such was not usually the case in this group. Evidence of continuing activity of a disease process for fourteen to forty days during the so-called latent period before the appearance of fever and arthritis was obtained from 9 of the patients. In each instance the erythrocyte sedimentation rate remained above 30 mm per hour. This course is to be contrasted with the usual course of acute hemolytic streptococcus

CASE 1—A 19 year old youth, who gave a past history of rheumatic fever at the age of 14, was admitted to the hospital on the first day of a type 19 hemolytic streptococcus sore throat. His subsequent course is presented in chart 1. The acute illness subsided rapidly after the administration of penicillin and sulfadiazine, the leukocyte count returned to normal and the erythrocyte sedimentation rate on the ninth day had fallen to 30 mm per hour. At this time he felt fairly well, but electrocardiographic evidence of carditis in the form of sharp inversion of the T waves in all leads was discovered. He was discharged from the hospital, and five days later the left ankle became painful. His symptoms became more severe over a period of six days, and fever appeared. At this time he reentered the hospital and was found to have an acute polyarthritis involving the knees and ankles. The temperature was 102 F, the erythrocyte sedimentation rate 28 mm per hour and the electrocardiogram indic-

tical with that obtained on the ninth day His disease became more active and ran the course of severe rheumatic fever with pericarditis The latter condition was little improved by the administration of large amounts of sodium salicylate The electrocardiogram remained abnormal for more than ninety days

Comment—This was a patient in whom definite evidence of activity of a disease process, in the form of a rapid erythrocyte sedimentation rate and carditis, was demonstrated to be present during the quiescent interval between the acute sore throat and the appearance of arthritis

These observations, together with others to be presented later, indicate that certain phases of the rheumatic state are initiated soon after the initial illness of the respiratory tract and that the conception of a latent period is in part erroneous In 3 of the 4 persons in whom a

new types of hemolytic streptococci, and these cases require special comment

Both types were present early in the initial illness of 1 patient, and the exact significance of their presence then is difficult to evaluate In 2, both of whom exhibited a true latent period, types of hemolytic streptococci different from that causing the initial illness were present in the throat at the time of the onset of arthritis It seemed possible that reinfection by this new strain might have incited the rheumatic process That this could be the case is suggested by the course of events in case 2, the clinical course of which is illustrated in chart 2

CASE 2—A 19 year old youth entered the hospital on the first day of an acute hemolytic streptococcus sore throat, caused by an organism of type 3, from which

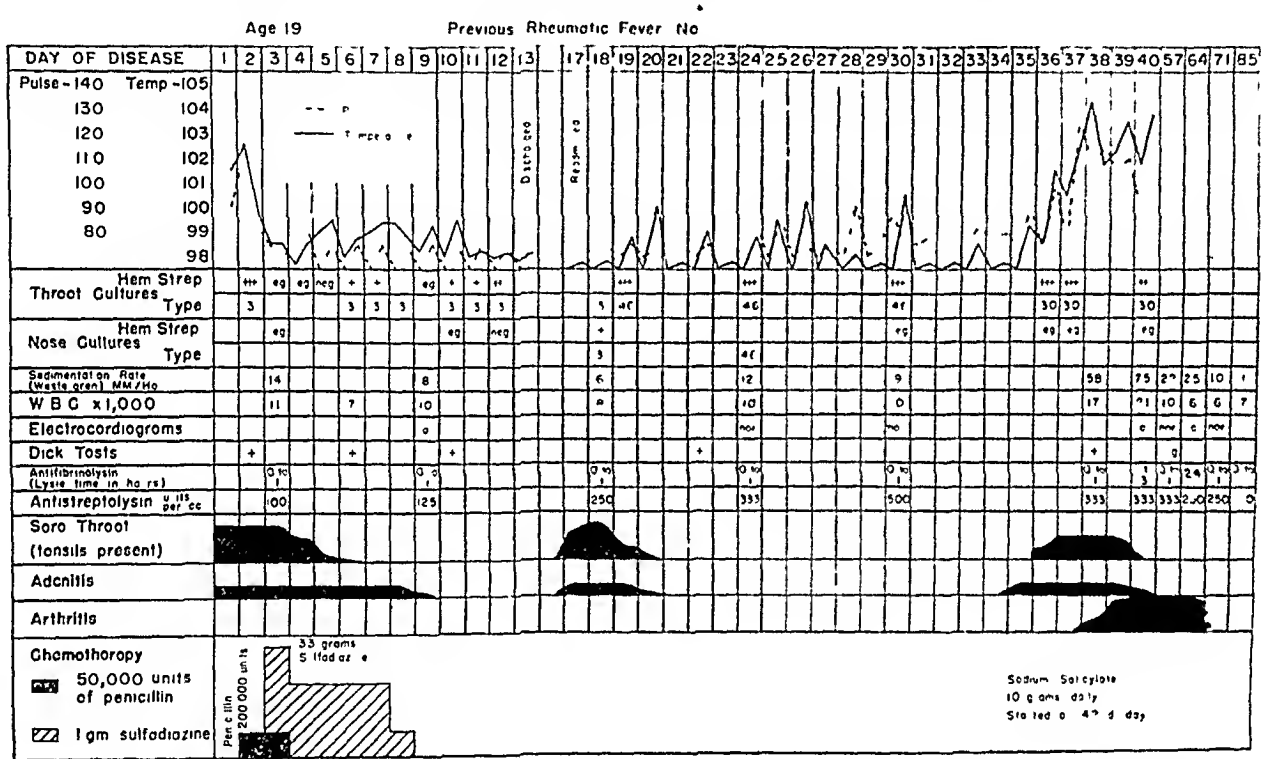


Chart 2—The clinical course of acute hemolytic streptococcus sore throat followed by rheumatic fever after two reinfections by different serologic types

definite latent period was observed, activation of the rheumatic disease may have been induced by a reinfection with a new type of hemolytic streptococcus (different from the one involved in the previous infection)

Reinfection by New Types of Hemolytic Streptococci—Rheumatic fever developed in 6 persons in whom infection by only one serologic type of group A streptococcus was demonstrated A past history of rheumatic fever was obtained for 2, and for 5 a definite latent period was absent Case 1, just cited, is an example of this type of reaction to streptococcic infection In 3 patients there was bacteriologic, and in 3 bacteriologic and clinical, evidence of reinfection by

he made an uneventful recovery after therapy with penicillin and sulfadiazine Nineteen days after the onset of the initial illness he reentered the hospital, suffering from another acute sore throat due to type 46 streptococci Recovery again occurred, and the erythrocyte sedimentation rate remained normal until two weeks later, when a sore throat due to a strain of type 30 developed High fever and severe polyarthritis appeared thirty-six hours later, and the subsequent course was that of rheumatic fever without evidence of carditis

Comment—Rheumatic fever developed within thirty-six hours after the last of three acute hemolytic streptococcus sore throats, each of which had been caused by a different serologic type

In 2 other cases, definite clinical as well as bacteriologic evidence of reinfection by new types on two or three occasions was obtained

In 1, arthritis appeared seven days after the last acute episode. The other was different, in that the erythrocyte sedimentation rate remained above 40 mm per hour for two weeks after two attacks of sore throat caused by types 30 and 36 and carditis was demonstrable by electrocardiography, but arthritis did not manifest itself until forty days after the subsidence of the second attack. A third strain, of type 19, was discovered in the pharynx during this interval.

These observations suggest that reinfection by hemolytic streptococci may be important in the pathogenesis of the rheumatic state. This possibility will be further discussed in another section.

Certain patients convalescent from group A streptococcal sore throat, with signs and symptoms similar to some of those observed in rheumatic fever but without arthritis, will now be described. Two hundred and twenty-seven, or 76.6 per cent of the whole group, including patients with every degree of initial severity of illness, made a rapid and complete clinical recovery, and the erythrocyte sedimentation rate was found to be less than 20 mm per hour three weeks after the onset of acute illness.

*Continuing Disease Without Arthritis or Carditis*—In 34 cases the erythrocyte sedimentation rate had not returned to normal by the end of the third week after the onset of the acute illness. No clinical signs of continuing disease were discovered in 20 of the patients, or 67 per cent of the total group, but in 14, or 47 per cent, definite evidence of an active process was obtained. This was manifested by fever, easy fatigability, anorexia and loss of weight and frequently was sufficiently severe to require continued rest in bed. Serial electrocardiograms in this group were normal.

*Continuing Disease with Carditis*—In 10.8 per cent of the group of 185 cases in which serial electrocardiograms were performed, or 20 cases, a syndrome similar to that just described was observed, with the difference that definite electrocardiographic evidence of carditis was discovered. In certain cases this consisted of prolonged and changing PR intervals, in others, of sharp inversions of the T waves, usually in all three leads, and in a few of a combination of these signs. Frequently, clinical evidence of a tissue reaction in the form of fever and malaise was present. Several men in whom striking electrocardiographic abnormalities were demonstrable for several weeks felt perfectly well.

Certain aspects of these cases deserve comment. A true latent period following the acute illness was observed in only 6 of these 20 cases. In this small group the erythrocyte sedimentation

rate returned to normal, and the patients were clinically well, later the sedimentation rate became more rapid, and the electrocardiogram, previously normal, was discovered to be abnormal. In the other cases, the sedimentation rate remained above 30 mm per hour after the initial illness, and frequently the patients presented clinical evidence of continuing disease. Electrocardiograms were obtained for 10 of these patients on the seventh to ninth days of illness and were found to be abnormal in 8. In several these changes persisted for two or three weeks. It is clear, therefore, that a latent period is usually absent when carditis of this type follows acute streptococcal sore throat and that evidence of the presence of carditis may be demonstrated soon after the termination of the acute initial illness.

Bacteriologic and, in 1 case, clinical evidence of reinfection by a new type of group A hemolytic streptococcus was discovered in 7 of these persons. In 1 this event occurred early in the illness, in the others, late. Among the latter were 4 of the 6 patients during whose illnesses a true latent period occurred. Study of 3 of these was sufficiently detailed to indicate that the termination of the quiescent period, with the appearance of an elevated sedimentation rate and carditis, was intimately associated with the reinfection.

In none of these persons did physical signs of pericarditis or endocarditis develop, but the period of observation was too short to exclude the possibility that valvular damage might occur.

#### THE FACTOR OF REINFECTION

In previous sections of this report it has been suggested that reinfection by a new type<sup>6</sup> of hemolytic streptococci may be of importance in the causation of nonsuppurative complications following hemolytic streptococcus sore throat. Further information on this point can be obtained by determining the incidence of these complications in the whole study group. These data are presented in the table.

Infection by only one type of hemolytic streptococci was demonstrated in 230 patients,

6 Emphasis has been placed on reinfection by a type of streptococcus different from that causing the initial disease, since evidence exists (Kuttner, A. G. and Krumwiede, E. Observations on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks. *J. Clin. Investigation* 23: 139, 1944) that a considerable type-specific immunity persists after recovery from hemolytic streptococcus infection. Relapse, if it can occur, should be equally effective in initiating the phenomenon of the poststreptococcal state.

A continuing disease, with or without carditis, followed the initial illness in 13.1 per cent of these patients, and rheumatic fever followed in 2.6 per cent. Two types were present in the throat during the initial acute illness in 16 and the frequency of complications was similar to that just described.

A new type was discovered to be present in large numbers in the throats of 38 patients two to three weeks after the onset of the initial illness. Continuing clinical disease, with or without carditis, was present in 22.6 per cent of these patients, and rheumatic fever was present in 5.3 per cent—an incidence approximately twice as great as that just described.

Definite clinical as well as bacteriologic evidence of a reinfection by one or more new types of streptococci was obtained in 12 cases. In 3, or 25 per cent, rheumatic fever developed, in 4, or 35 per cent a severe clinically evident continuing disease in 1 instance with carditis.

It is clear, on the basis of these observations, that rheumatic fever is but one manifestation of a pathologic process instituted by infection with hemolytic streptococci. Certain patients after such an infection present only signs of continuing tissue reaction in the form of a prolonged erythrocyte sedimentation rate for several weeks, in others this sign is associated with fever, malaise, loss of weight and other clinical signs of an active disease process. Electrocardiographic evidence of carditis may be discovered in a third group of patients showing signs similar to those just described. Finally, arthritis will be observed in a few instances, some of the patients having a mild disease with low grade fever and others a severe illness with signs of pericarditis, endocarditis and the other manifestations of typical rheumatic fever.

It seems impossible to establish adequate criteria for the accurate division of these various late complications of streptococcic disease into

*Relation of Reinfection by a New Type of Group A Hemolytic Streptococci to the Incidence of Nonsuppurative Poststreptococcic Complications*

	Continuing Disease		Continuing Disease and Carditis		Rheumatic Fever		Total Cases with Serial Electrocardiograms	Total Cases		Total with Complications Per centage
	Number	Per centage	Number	Per centage	Number	Per centage		Number	Per centage	
Monotype infections	10	13	12	33	0	2.6	136	230	77.8	15.7
Early reinfection	0	0.0	1	11.0	1	6.2	9	16	5.1	17.2
Late reinfection, bacteriologic	1	2.6	6	30.0	2	5.3	30	38	12.6	27.0
Late reinfection, bacteriologic and clinical	3	25.0	1	10.0	3	25.0	10	12	4.0	60.0
Total complications	14	4.7	20	10.8	12	4.1	185	296	100.0	19.6

Serious late complications occurred in 60 per cent of this small group of cases.

It is obvious that the numbers of cases are too small to permit accurate statistical analysis. Nevertheless, the increased frequency of nonsuppurative disorders in patients in whom evidence of reinfection by a new type of hemolytic streptococci was discovered suggests that this event may be causally related to the development of these complications.

#### COMMENT

The study just described of a large number of persons suffering from various types of illness of the respiratory tract indicates that the syndrome known as rheumatic fever occurs only as a sequel to infection by group A hemolytic streptococci. This is in accord with previous information obtained indirectly but appears to be more definitive. One objection to the general acceptance of this etiologic relationship in the past has been the fact that hemolytic streptococcic respiratory disease was extremely common but that rheumatic fever was a rare complication.

separate groups. Carditis with and carditis without arthritis must be regarded as comparable disorders and both appear to be related to arthritic disease without carditis. Since arthritis has been demonstrated without carditis and carditis has been demonstrated without arthritis there appears to be no valid reason for concluding that examples of continuing disease in the absence of both of these clinical phenomena are unrelated to the first two types of disorder.

Because of these difficulties and because evidence of carditis, the most serious complication was observed most frequently in the absence of arthritis, it would seem to be desirable to discourage the emphasis placed on the rheumatic fever syndrome and to begin to think in terms of the complications occurring after streptococcic infection, which might well be grouped under the term, "poststreptococcic state." Such disorders as rheumatic fever, postscarlatinal arthritis and atypical rheumatic fever could be considered as a single entity. Furthermore, the fact that serious nonarthritic complications may follow streptococcic infections would be emphasized.

These observations, though more detailed, are in accord with the concept developed over the last thirty years that nonsuppurative disease<sup>7</sup> associated with fever, arthritis, adenitis, nephritis and other signs and symptoms may be a sequel to hemolytic streptococcal infection.

Unfortunately, this study has not determined whether poststreptococcal carditis in the absence of arthritis may lead to valvular heart disease. The close similarity between such cases of carditis alone and cases of carditis with arthritis suggests that it would, particularly if repeated similar episodes should occur in any patient. It should also be emphasized that previous studies of rheumatic fever have shown that the physical signs indicating the presence of a lesion of the cardiac valves may not appear for many months, although electrocardiographic and clinical evidence of carditis may be demonstrated early in the disease.

The precise mechanism involved in the development of these late streptococcal complications, particularly of rheumatic fever, has been a matter of speculation for many years. The most widely accepted suggestion proposes that products of the hemolytic streptococcus are distributed widely throughout the body at the time of the acute infection, becoming "fixed" in various tissues. Later, as antibodies develop as the result of infection, an antigen-antibody combination occurs on the cell surfaces, exciting the rheumatic syndrome and presumably the other nonsuppurative complications of streptococcal disease.<sup>8</sup> This rather simple hypothesis has been modified by Swift and others to include a factor of chronic streptococcal infection on the basis of faulty immunity as essential to the development of hypersensitivity of the tissues.<sup>9</sup>

Such a process, rather analogous to serum sickness, presupposes that a single infection by hemolytic streptococci may establish the pathologic condition. Little actual evidence is available in support of this view. The fact that rheumatic fever rarely occurs in children less than 3 years old although streptococcal disease is common in that age group suggests that the primary infection by these organisms may be incapable of inducing the phenomenon of the poststreptococcal state. Bearg, Boisvert, Darrow, Powers and Trask<sup>10</sup> have emphasized the

fact that the tissue reaction to streptococcal infection is altered by the initial infection in children, and Schlesinger<sup>11</sup> has suggested that repeated infection by hemolytic streptococci may be necessary for the development of rheumatic fever.

This study has further altered the older concept by showing that a true latent period is uncommon in instances of carditis and rheumatic fever and that when it is demonstrated reinfection by a new type of streptococcus has frequently occurred. Electrocardiographic evidence of carditis not only was observed long before the appearance of arthritis but was frequently present soon after the end of the acute suppurative phase of the disease. It therefore seems clear that some phases of the tissue reaction involved in the rheumatic or poststreptococcal state begin early in the so-called latent period, suggesting that a direct toxic action of the products of the streptococcus on the involved structures may be responsible for these disorders. This seems unlikely, however, when it is considered that 80 per cent of all infected persons, including many of the most seriously ill, escape these late complications.

Furthermore, suggestive evidence has been presented which indicates that repeated closely spaced infections by different types of group A streptococci are more likely to incite late nonsuppurative complications than is a single infection. It seems desirable, therefore, to return to and modify the original concept that these pathologic processes are the result of an antigen-antibody reaction. This is particularly appropriate since recent studies by Rich and Gregory have demonstrated that microscopic lesions similar to those observed in rheumatic fever may be reproduced in rabbits by the production of serum sickness in these animals.

Because reinfection with new types of hemolytic streptococci frequently preceded rheumatic fever and continuing disease, an attractive hypothesis presents itself.

It may be supposed that these late complications occur in patients who have suffered previous streptococcal infection and whose tissues have been sensitized to some fraction or product of the hemolytic streptococcus by antibodies developed at that time. Subsequent infection

7 Keefer, C. S. The Late Non-Suppurative Disorders of Hemolytic Streptococcal Diseases, *Texas State J. Med.* **35** 457, 1939.

8 (a) Schlesinger<sup>11b</sup> (b) Swift, H. F. Rheumatic Fever, *J. A. M. A.* **92** 2071 (June 22) 1929.

9 Swift, H. F., and McEwen, C. Rheumatic Fever, in Christian, H. A. *Oxford Medicine*, New York, Oxford University Press, 1938. Coburn, A. F. Observations on the Mechanism of Rheumatic Fever, *Lancet* **2** 1025, 1936.

10 Bearg, P. A., Boisvert, P. J., Darrow, D. C., Powers, G. F., and Trask, J. D. "Streptococcosis" and "Streptococcal Fever," *Am. J. Dis. Child.* **62** 431 (Aug.) 1941.

11 Rich, A. R., and Gregory, J. E. Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, *Bull. Johns Hopkins Hosp.* **73** 239, 1943.

would then find the tissues in a hyperreactive state, and the syndromes of the poststreptococcal state could be established. This hypothesis is in accord with the known facts that horse serum sickness in human beings who have received a previous injection of similar serum is more severe and appears in an accelerated form. The presence of carditis early in the latent period and the explosive appearance of arthritis twenty-four to forty-eight hours after the last of repeated streptococcal infections of the respiratory tract could be readily explained on this basis. It is not entirely clear why arthritis followed the first demonstrable carditis at such a long interval in certain cases.

It is possible that a degree of sensitivity of the tissues adequate to permit the development of rheumatic fever is usually obtained only by repeated, closely spaced infections. Evidence of such reinfection was obtained in 6 of 12 patients exhibiting this syndrome, and in 3 two reinfections occurred. In another study, by van Ravenswaay,<sup>12</sup> the type of streptococcus causing the initial illness was determined for 36 persons in whom rheumatic fever subsequently developed. At that time, a type different from that originally present was discovered in the throats of 28.

While the nonarthritic complications of streptococcal disease frequently, and arthritis occasionally, followed single infections, it is probable that all these men had suffered from previous unrecognized streptococcal respiratory infections, although no evidence can be presented to prove that the infections had occurred. In two arthritic patients, a past history of rheumatic fever suggested that an abnormal sensitivity of the tissues to the products of the streptococcus had been previously established.

The fact that some type of nonsuppurative complication failed to develop in all persons in whom bacteriologic evidence of reinfection was obtained may have been due to an inadequate sensitivity of the tissues and to a necessity for further reinfections. These causes appeared to be factors in 2 cases. It must also be borne in mind that a tissue reaction does not invariably occur when a new type of streptococcus gains lodgment in the throat—a fact that is emphasized by the high incidence of complications in the small group in whom definite clinical reinfection took place.

If it be assumed, as this study indicates, that the arthritic phase of the poststreptococcal state

is a special reaction based on extreme hypersensitivity often associated with repeated reinfection, the notable discrepancies between the reported incidence of chronic rheumatic heart disease and of clinical rheumatic fever can be explained. Reinfection may occur on enough occasions in certain areas to excite the development of heart disease but not of arthritis. In other areas, in which streptococcal disease is much more common, reinfection would be a sufficiently frequent event to permit the appearance of rheumatic fever.

The supposed individual resistance to rheumatic fever may be more apparent than real, because it is possible that repeated infection by hemolytic streptococci at suitable intervals will incite the rheumatic process in many, if not all, persons. The rarity of this disease may be explained by the fact that many persons are resistant to infection by these organisms and that others escape the frequent reinfections necessary to induce, in them, a sufficiently great sensitivity of the tissues.

In summary, it seems not unreasonable, on the basis of these observations, to make the following assumptions as the basis for further investigation: (1) that rheumatic fever is invariably induced by infection by group A hemolytic streptococci, (2) that this syndrome is but a part of the whole complex involved in the poststreptococcal state, (3) that these clinical manifestations are the result of altered sensitivity of the tissues to products of the hemolytic streptococcus and (4) that repeated infection with different types of hemolytic streptococci may be necessary for the development of these disorders.

If this working hypothesis is acceptable, then the following statements appear to be correct: (1) that sensitivity of the tissues must occur to some fraction or product of the hemolytic streptococcus and (2) that this fraction or product must be common to all types of group A streptococci.

It would seem desirable, therefore, to obtain these substances in highly purified form and to determine whether they have induced the formation of circulating antibodies and whether the tissues of rheumatic persons are sensitive to them. Similar studies in the past have contributed interesting and suggestive information, but the crude nature of the test substances and the failure to perform quantitative studies have lessened their importance.

Such investigation might lead to techniques which would permit the determination of dangerous streptococcal hypersensitivity and to possible preventive or therapeutic measures.

<sup>12</sup> Van Ravenswaay, A. C. The Geographic Distribution of Hemolytic Streptococci. Relationship to the Incidence of Rheumatic Fever, *J. A. M. A.* 126:486 (Oct. 21) 1944.

# CHARACTERISTIC VASCULAR PATTERN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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During the grading of the basal vascular tone<sup>1</sup> of normal persons and patients with various diseases by a method recently described by two of us,<sup>2</sup> it was found that patients with rheumatoid arthritis had a characteristic basal vascular tone which explained certain clinical features of the disease. In some patients the diagnosis of rheumatoid arthritis first suggested itself by a characteristic vascular behavior, a dissociated response between the affected and the unaffected digits not ordinarily seen where there is no arterial occlusion.

Since there was no objective information as to the grade of tone in the peripheral vessels of patients with rheumatoid arthritis, the vascular responses of a group of such patients were studied by the method described in this paper.

It is significant that in all the patients with rheumatoid arthritis subsequently studied there was a consistently high grade of basal vascular tone in contrast to that of a large group of normal persons tested, in whom a wide range of low and high vascular tone was found.

Vasospasm appears to be a predisposing factor in this condition—a fundamental vascular pattern, which, together with heredity, susceptibility to infection, chilling and other factors, permits the development of rheumatoid arthritis. It seems more than coincidental that this condition usually is first manifested at the site of greatest vascular tone, namely the digits, and it is suggested that treatment such as that given in other vasospastic disorders, in which emphasis is directed toward vasodilation by interruption of hyperactive vasoconstrictor reflexes by para-

vertebral block or by caudal anesthesia, may be of benefit for these patients.

Other studies on the capillaries and on the periarthritic tissues of patients with rheumatoid arthritis have given conflicting information as to what vascular responses are typical in this condition. Unlike ours, these studies were not done under basal conditions and were primarily concerned with the affected extremities. However, these conflicting observations can be correlated when their relation to our study is considered. Our observation of a high grade of vascular tone in the less affected extremities together with vasodilation in the extremities in which the arthritic process is active brings into focus the contradictory views on this aspect of the condition obtained from previous observations of the circulation in these patients.

## METHOD

The method for grading vascular tone has been described in detail in a recent report.<sup>2</sup> Briefly, this is done by determining the degree of vasoconstriction and vasodilation, as reflected in temperatures of the fingers and toes, during a cool period and during the application of moderate heat to the trunk in a constant temperature room at 20 C. Reflex heat is applied by means of electric pads set at moderate heat and two blankets. The patient is unclothed except for a light hospital gown and is under basal conditions, having omitted the meal before the test and any medication or hot bath. If the fingers cool rapidly, falling below 25 C fifteen minutes after the start of the test, and if vasodilation with reflex heat is difficult, the person has a high grade of vascular tone, or is vasospastic. If the fingers cool slowly or not at all, remaining above 25 C fifteen minutes after the start of the test, the person has a low grade of vascular tone. This method has enabled us to determine the basal vascular tone of over 400 persons (normal persons and patients with rheumatoid arthritis and other diseases). For the purpose of this study the basal vascular tone of 15 patients with rheumatoid arthritis was determined. The ages of the 15 patients varied from 14 to 65 years. Thirteen were females, and 2 were males. The duration of the arthritic process varied from six months to thirty-two years. All the patients were ambulatory.

The type of vascular tone in the rheumatoid arthritis patients was based on the vascular response in the uninvolved or less involved digits and led to the interesting observation that there was in some persons a different or dissociated response in the involved and the uninvolved digits.

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1 Vascular tone is the ability of blood vessels to constrict and to dilate.

2 Naide, M., and Sayen, A. A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis, *Am J M Sc* 207 606 (May) 1944.

## RESULTS

Two significant observations emerged from this study of vascular tone in patients with rheumatoid arthritis. First, 14 of these 15 patients proved to have a high grade of basal vascular tone. The fifteenth patient had definite involvement of all of the digits, so that the basal vascular tone could not be obtained. In the 14 rheumatoid arthritic patients in whom the basal vascular tone could be determined, the temperature in the fingers fell rapidly in the temperature-controlled room or was already low at the start of the test. The responses of digital temperature of these patients was such as to label them the vasospastic type. Second, there was a "dissociated" vascular response of uninvolved and involved digits, which first suggested the diagnosis of early rheumatoid arthritis in 2 patients, which was later confirmed by roentgenograms, studies of the sedimentation rate and the subsequent clinical courses.

Whereas in most persons vasoconstriction and vasodilatation occur in the toes of both feet or in the fingers of both hands almost simultaneously, in some of the patients with rheumatoid arthritis the processes occurred in a different manner, a finger or toe involved by the arthritic process (early as well as late) usually remained warm longer during the cool period than did an uninvolved digit. When a large joint was involved, the digits of that extremity did not vasoconstrict as easily as did the digits in the opposite extremity if the latter was unaffected or affected to a lesser degree. Furthermore, the vessels of an affected part frequently dilated more readily with reflex heat. The arthritic process, probably as a result of inflammation, seemed to cause vascular relaxation to a greater degree in the affected digits. Observation of this dissociation led to the diagnosis of early rheumatoid arthritis in the 2 patients just mentioned, who were at first suspected of having a vascular condition resembling acrocyanosis, or Raynaud's disease. The diagnosis of rheumatoid arthritis suggested by observation of this dissociated response during the test for vascular tone was later confirmed.

Several other conditions may also give such a dissociated response during the test for vascular tone. These are usually readily differentiated from rheumatoid arthritis. They include hemiplegia, pressure on the brachial plexus by cervical rib, and pressure seen in scalenus anticus syndrome.

One other observation made in this study was that there was much more frequent and a much greater degree of perspiration in the distal

phalanges of both hands and feet during the heating period of the test for vascular tone in patients with rheumatoid arthritis than in normal persons.

## COMMENT

*Relation of Observations to Possible Cause of Rheumatoid Arthritis*—From a study of the vascular tone of these patients with rheumatoid arthritis, the response was such as to indicate that they were in the vasospastic group before this disease developed. The high grade of vascular tone was found in uninvolved digits or extremities. The vessels in the extremities involved by the rheumatoid arthritic process were not as vasospastic as those in unaffected extremities.

We do not yet know all of the factors that may influence vascular tone or why certain persons fall into the group with low vascular tone and others into the group with high vascular tone. The term "vasomotor tone" is not used here, because the tone of blood vessels not only is influenced by the sympathetic nervous system but depends in part on the intrinsic tone of the wall of the blood vessel itself, on pressor substances and on other factors. In many persons sympathetic tone is the predominant factor in determining the grade of vascular tone. The presence of larger than average pupils, measured with a pupillometer in a constant source of light in patients with rheumatoid arthritis suggests that increased sympathetic tone accounts for the high vascular tone as well as for the increased sweating in these patients.

All persons are subjected to vasoconstriction in the winter, but there is a more prolonged and intense vasoconstriction in vasospastic persons, who respond so readily to cold. The patient with high vascular tone will respond by vasoconstriction more readily than others to emotional stimuli and pain as well as to cold. The higher the vascular tone in a person, the shorter is the duration of vasodilatation following the application of heat. Grant, Mudd and Goldman<sup>3</sup> found that in human beings chilling of the body surface causes vasoconstriction and ischemia in the mucous membranes of the palate, pharynx and palatine tonsils. They also found that chilling of the body results in proliferation of organisms present in the mouth and in the production of sore throats and slight constitutional symptoms. Since the vessels of persons with a high grade of vascular tone constrict more readily to cold, it would appear that patients with rheu-

<sup>3</sup> Grant, S., Mudd, S., and Goldman, A. A Further Experimental Study on Excitation of Infections of the Throat, *J. Exper. Med.* **32**: 87 (July) 1920.

matoid arthritis who have this tendency may be likely to have infections of the upper respiratory tract more frequently than persons with a low grade of vascular tone. Vasospasm appears to be a predisposing background for rheumatoid arthritis. It is conceivable that without this underlying factor in such patients, rheumatoid arthritis might not develop.

Freyberg and his associates,<sup>4</sup> in a study of 25 patients with rheumatoid arthritis and controls, found that emotional stress produced a drop in skin temperatures indicative of a change in circulation. The differences noted were suggestive but were not conclusive. They concluded that the significance of emotional stress appeared worthy of further investigation in rheumatoid arthritis. Our studies indicate that if a large number of their control subjects were in the normal vasospastic group, one then would not expect significant differences between this group and their patients with rheumatoid arthritis. Had their controls been persons with a low grade of vascular tone, there would have been a significant difference in response between them and the patients with rheumatoid arthritis.

Myers<sup>5</sup> noted that no vasoconstriction was found in the periarthritic tissues in persons with rheumatoid arthritis. This observation agrees with our observations of relaxed vessels in involved digits and extremities.

Kovacs, Wright and Duryee<sup>6</sup> observed a noticeable diminution in the volume of the peripheral circulation with a great reduction in the number of capillaries in the peripheral tissues in patients with rheumatoid arthritis. The thin, shiny, atrophic skin with cold, pale, clammy hands and feet and the cutaneous pigmentation in persons with rheumatoid arthritis results from an impairment of circulation; however, this deficiency must be contrasted sharply with the greatly increased blood supply in the articular tissues. Although the extremities are usually cold and clammy, the affected joints may show an increase in local heat.

Hench<sup>7</sup> was unable to find any consistent alteration in the size of the capillaries or in capillary flow in a large number of cases of rheumatoid arthritis and degenerative diseases. Fur-

thermore, it is known that rheumatoid arthritis is not more common in extremities with organic arterial occlusion. Conclusions drawn from patients with organic arterial disease as to the influence of circulation on arthritis are valueless. The effect of vascular spasm differs completely from that of simple arterial occlusion. Not only the arteries but also the veins are involved in the spasm.

It is definitely known that veins can constrict and frequently do so. For example in thrombophlebitis a paravertebral block is done to relax venospasm as well as arterial spasm. Any obstruction to venous return, whether this is due to an obstruction of veins or to venous spasm may result in edema. There is scanty information concerning the flow of venous blood in the proximity of joints in rheumatoid arthritis. The patient with rheumatoid arthritis is a vasospastic person, and in many persons the veins as well as the arteries participate in the vasoconstriction. An increase in venous tone outside the area of the inflamed joint in the presence of decreased arteriolar tone secondary to local inflammation in the proximity of joints could result in swelling in that region. Local inflammatory vasodilatation might predispose to local edema in the vicinity of affected joints in the presence of a generalized peripheral vasospasm.

*Relation of Observations to Clinical Picture of Rheumatoid Arthritis*—The observation that a high grade of vascular tone is a basic vascular state in patients with rheumatoid arthritis may explain certain clinical features of the disease. The frequent presence of cold hands and feet, increased sweating, symptomatic improvement with vasodilating procedures and perhaps aggravation of the disease by emotional upsets or stress can be readily explained on the basis of a high grade of vascular tone. The blood vessels of normal persons with high basal vascular tone constrict readily to cold and emotional strain. These persons have cold feet and, often cold hands. They usually sweat more easily either because of increased sympathetic tone or because of decreased ability to eliminate heat through vasodilatation.

If one tells a normal person with a high basal vascular tone that he is to have an injection there occurs an immediate drop of 2 to 6 degree (centigrade) in finger temperature, with a considerable reduction in peripheral blood flow. This behavior is equally characteristic of

4 Patterson, R. M., Craig, J. B., Waggoner, R. W., and Freyberg, R. H. A Psychosomatic Study of Rheumatoid Arthritis, *Univ. Hosp. Bull., Ann Arbor* 8:86 (Oct.) 1942.

5 Myers, W. K. Etiology of Rheumatoid (Atrophic) Arthritis, *M. Ann. District of Columbia* 5:203 (July) 1936.

6 Kovacs, J., Wright, I. S., and Duryee, A. W. Surface Temperature and Minute Vessels of Skin in Arthritis, *J. A. M. A.* 100:1018 (April 1) 1933.

7 Hench, P. S., in discussion on Kovacs, J. The Peripheral Blood Circulation in Chronic Arthritis and the Influence of Vasodilators, *J. A. M. A.* 103:180 (Dec. 8) 1934.

patient with rheumatoid arthritis who also has a high basal vascular tone. The high basal vascular tone in patients with rheumatoid arthritis is not abnormally high. It is simply the grade of vascular tone which is found in from 30 to 40 per cent of normal persons.

In testing over 400 subjects without rheumatoid arthritis, increased vascular tone was found much more commonly in women than in men. Clinically there are many more women than men who give a history of cold hands and feet. It is interesting and perhaps significant that rheumatoid arthritis occurs from two and a half to four times as frequently in women as in men and that the occurrence of rheumatoid arthritis is most frequent in the fingers and toes, the sites of greatest vascular tone in the body. These are the sites selected by other conditions associated with vasospasm, namely, Raynaud's disease and scleroderma. Rheumatoid arthritis is more common in cold countries, where vasoconstriction would be expected, and is much less frequent in warm regions, where vasodilatation is the normal state. Changes in barometric pressure may also influence the vascular tone as well as other factors, such as marked variations in temperature.

*Relation of Observations to Treatment of Rheumatoid Arthritis*—Our observations suggest that frequent and persistent attempts to produce reflex vasodilatation, as with warm tub baths and by heating the trunk, may tend to relax the tone of peripheral vessels. Repeated lumbar paravertebral block with procaine hydrochloride may prove to be worth while for some patients with persistently painful joints in the lower extremities. Periods of continuous caudal anes-

thesia for persistent articular pains in the lower extremities may be useful for prolonged vasodilatation and analgesia. The symptomatic benefit obtained by some patients with rheumatoid arthritis from a constant warm, dry climate might be explained on the basis of constant peripheral vasodilatation. Ghormley and Silverglade<sup>8</sup> have stressed the efficiency of systemic heating in contrast to local heating in producing generalized vasodilatation. Also, since these persons are chilled easily, the necessity of proper clothing in cold weather must be stressed.

#### SUMMARY

A study of the vascular responses of patients with rheumatoid arthritis under basal conditions disclosed a characteristic vascular pattern. The basal vascular tone in these patients is high. Their peripheral vessels are easily constricted. This high vascular tone may explain certain clinical features of the disease and may be one of the basic factors in predisposing persons to rheumatoid arthritis and to flare-ups of the condition after emotional upsets and exposure to cold. It may also explain the causalgia-like symptoms, such as hyperesthesia and severe burning pain and a lower threshold for pain, which would maintain a reflex cycle of pain and vasoconstriction.

A characteristic dissociated type of response during the test for vascular tone has permitted early diagnosis of rheumatoid arthritis in some patients.

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<sup>8</sup> Ghormley, J. W., and Silverglade, A. Circulation of Joints of Chronic Arthritis, New York State J. Med. 39 1489 (Aug. 1) 1939.

# GALLBLADDER DYE (IODOPHTHALEIN SODIUM)

## EFFECT OF INTRAVENOUS INJECTIONS ON CORONARY FLOW, BLOOD PRESSURE AND BLOOD COAGULATION

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The dangers of intravenous cholecystography have been cited in the literature since 1925. At this time, Graham, Cole and Copher<sup>1</sup> noted the incidence and symptoms of various disturbances occurring in connection with the use of intravenous injections of gallbladder dye.

Palmer and Ferguson,<sup>2</sup> in 1933, reviewed the literature on reactions and contraindications to intravenous cholecystography. Their conclusion was that the chief contraindications are cardiovascular (cardiac decompensation and angina

contraindicated in hypertonia and hypotonia and in every case in which there is the slightest suspicion of coronary insufficiency or impending coronary spasm).

In 1939, Guignard and Nemours-Auguste<sup>4</sup> reported an occurrence of syncope, with disappearance of the pulse and loss of urine and feces, following intravenous cholecystography.

It is the purpose of this paper to present 2 cases of anaphylactic shock without coronary occlusion and 2 cases in which coronary occlu-

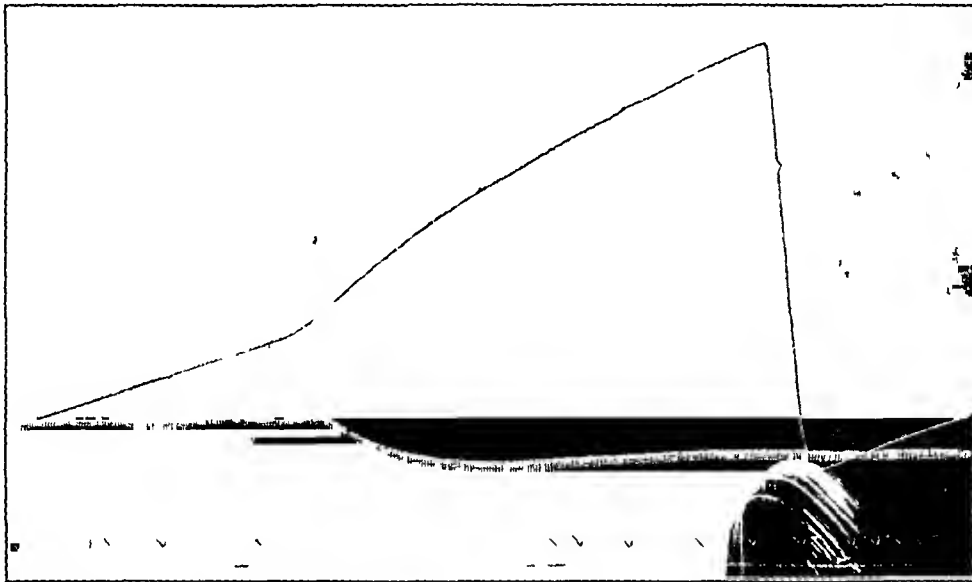


Fig 1—Effect of intravenous injection of iodophthalein sodium on coronary flow and blood pressure in the dog

pectoris or coronary sclerosis). In 1938, Lutz and Seyfried<sup>3</sup> published an article on corroboration by autopsy of a clinical diagnosis of sudden heart failure in the presence of coronary sclerosis in a 68 year old man who had been given gallbladder dye intravenously a few minutes before death. The conclusion of Lutz and Seyfried was that intravenous cholecystography is

sion occurred after administration of iodophthalein sodium. I also present the result of my experiments with the drug on both dogs and human beings.

### REPORT OF CASES

#### 1 *Anaphylactic shock from intravenous injections of iodophthalein sodium*

CASE 1—F W was a 45 year old man with known gastrointestinal allergy. After being given 1 cc of the gallbladder dye (3 Gm diluted with 50 cc of isotonic solution of sodium chloride), he noted a feeling of warmth in his arms, tinnitus and pounding in his head and became unconscious. His pulse was so weak that it was indiscernible, and the blood pressure could not

1 Graham, E A, Cole, W H, and Copher, G H. Cholecystography. The Use of Sodium Tetraiodophenolphthalein, *J A M A* 84:1175-1177 (April 18) 1925

2 Palmer, W L, and Ferguson, A N. Intravenous Cholecystography. Reactions and Contraindications, *Tr A Am Physicians* 48:385-397, 1933

3 Lutz, W, and Seyfried, H. Gefahren der intravenösen Cholezystographie, *Munchen med Wchnschr* 85:1019-1020 (July 8) 1938

4 Guignard and Nemours-Auguste. Accident grave à la suite d'une injection intraveineuse de tétraiode, *Arch d mal de l'app digestif* 29:211-213 (Feb) 1939

be detected. The patient was given 1 cc of 1,000 solution of epinephrine hydrochloride subcutaneously and placed in the Trendelenburg position. After he regained consciousness, his blood pressure was 108 systolic and 80 diastolic. He complained immediately of substernal pain, which persisted in spite of an intravenous injection of a solution of  $3\frac{3}{4}$  grains (0.24 Gm) of theophylline ethylenediamine. Twenty-four hours later, his blood pressure was 132 systolic and 80 diastolic, and forty-eight hours later it was 140 systolic and 84 diastolic. Serial electrocardiograms showed no diagnostic deformities.

CASE 2—B. G. was a 40 year old woman with no history of allergy, who immediately after injection of the dye presented a picture of shock. The pulse was thin and thready, she did not respond to external stimuli, and the blood pressure could not be detected. Epinephrine, in addition to the usual shock therapy, was given, and she responded. She did not complain of thoracic pain.

TABLE 1—Effects of Intravenous Injections of Iodophthalein Sodium on Dogs

	Coronary Flow Cc	Blood Pressure	Pulse Rate
Dog 1 Weight 11.6 Kg			
Control	0.51	31/27	144
50 seconds after 500 mg dye	1.17	24/20	150
Dog 2 Weight 10 Kg			
Control	1.26	57/34	123
50 seconds after 500 mg dye	2.70	41/36	123
Control	1.62	52/47	114
25 seconds after 250 mg dye	2.62	41/36	123
Control	1.80	47/40	120
30 seconds after 175 mg dye	2.16	45/40	120
Dog 3 Weight 8.2 Kg			
Control	0.51	20/17	111
20 seconds after 500 mg dye	1.44	14/10	105
Dog 4 Weight 9 Kg			
Control	1.62	50/38	117
35 seconds after 400 mg dye	2.68	30/26	102
Control	1.17	34/32	90
35 seconds after 230 mg dye	1.80	29/26	90
Control	1.44	23/18	93
50 seconds after 115 mg dye	2.25	22/17	78
Control	1.89	24/20	90
50 seconds after 75 mg dye	2.25	23/19	99
Control	2.34	23/19.5	105
45 seconds after 50 mg dye	2.70	23/18.5	108

## 2. Coronary occlusion following the intravenous injection of gallbladder dye

CASE 3 (from Wesley Memorial Hospital, where intravenous cholecystography was employed)—C. A. Y. was a 55 year old man with a history of angina pectoris, who was given an intravenous injection of iodophthalein sodium. Immediately after the dye was given, he had a severe attack of dyspnea, pain in his arms and a feeling of constriction in his chest and of faintness. His blood pressure taken two days previously was 176 systolic and 102 diastolic, but after the gallbladder dye was given, it was 140 systolic and 90 diastolic. Ten minutes later, it had risen to 180 systolic and 110 diastolic. Serial electrocardiograms showed changes in the T wave compatible with infarction. His white blood cell count was 22,400 the day after the dye was injected. His sedimentation rate two days before the dye was given was 20 mm in one hour, it was 23 mm the day after injection of the dye. His temperature rose 1 degree above normal the day after the gallbladder dye was given.

## 3. Coronary occlusion following the oral administration of gallbladder dye

CASE 4 (from St. Luke's Hospital)—C. H. W. was a 65 year old man who had a history of angina pectoris. He was given gallbladder dye orally and one hour later had an acute coronary occlusion, with a drop in blood pressure from 128 systolic and 102 diastolic to 60 systolic and 30 diastolic. An electrocardiogram indicated an infarction of the posterior wall. The patient died fourteen days later.

## EXPERIMENTAL STUDIES

4. Experiment on Dogs—The Morawitz cannula method of measuring coronary flow was employed. I feel that this method is valuable for judging the comparative result of flow. The dogs were anesthetized.

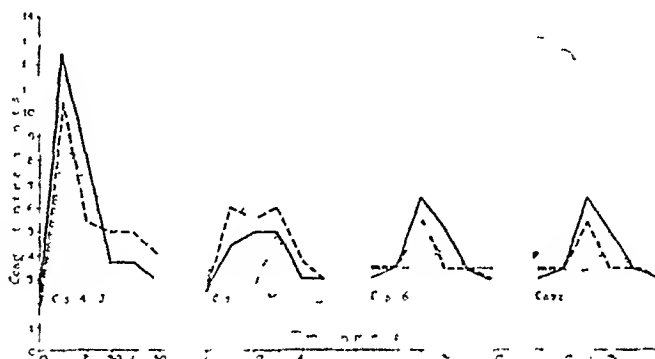


Fig. 2—Coagulation times of 4 patients after intravenous injections of iodophthalein sodium. Ten milligrams of heparin was injected intravenously before the gallbladder dye was injected (dotted line) as a control, five hours after the gallbladder dye was injected (broken line) and twenty-two hours after the gallbladder dye was injected (solid line).

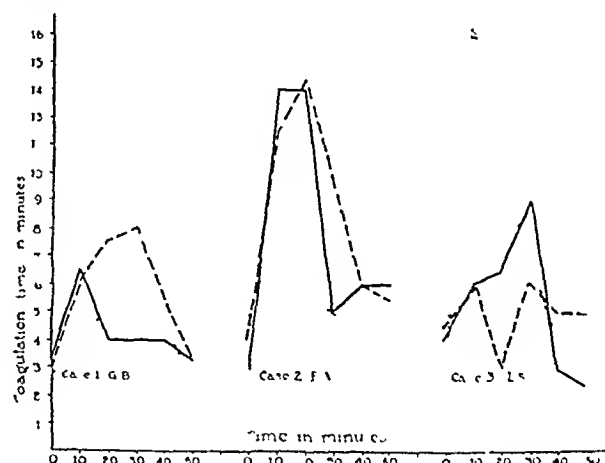


Fig. 3—Coagulation times of 3 patients after intravenous injections of iodophthalein sodium. Ten milligrams of heparin was injected intravenously before the gallbladder dye was injected (dotted line) as a control, five hours after the gallbladder dye was injected (broken line) and twenty-two hours after the gallbladder dye was injected (solid line).

with dial (5,5-diallylbarbituric acid), 0.6 cc per kilogram of body weight, an artificial respiration setup was established, and the carotid artery was cannulated for intravenous administration of the drugs used. The dogs were heparinized. The Morawitz cannula was then inserted into the coronary sinus. Iodophthalein sodium was administered intravenously in a dose proportionate to that given human adults, 3 Gm in 24 cc of water for a 155 to 160 pound (70 to 73 Kg) adult. The results are shown in figure 1 and table 1.

The conclusion reached as the result of these experiments on dogs is that the intravenous injection of iodophthalein sodium produces a fall in blood pressure and increases coronary flow

5 *Experiments on Human Subjects*—The effect of intravenous injections of iodophthalein sodium on the coagulability of the blood was determined for 7 patients by means of the heparin tolerance test described by de Takats<sup>5</sup>

A control heparin tolerance curve was made for each patient before the intravenous injection of gallbladder dye was given. A curve was made at the end of five hours and another at twenty-two hours after the dye was administered. The results of these tests are shown in figures 2 and 3. A summary of the charts shows that, in the 7 patients studied there was prolonged coagulation time in 4, both at five hours and at twenty-two hours after the iodophthalein sodium was administered. In 3, there was a decreased coagulation time, as indicated by the heparin tolerance curve.

Studies of the blood pressure were done prior to the injection of gallbladder dye, immediately after the dye was injected and at five hour and twenty-two hour intervals. There was noted a drop in blood pressure in 5 patients, while 2 patients' pressures remained the same (table 2).

#### CONCLUSIONS

1 Iodophthalein sodium produces an increase in coronary flow in dogs.

2 Intravenous injections of iodophthalein sodium produce a drop in blood pressure, both in dogs and in human beings.

5 de Takats, G. Heparin Tolerance, *Surg., Gynec & Obst.* 77 31-39 (July) 1943

3 The drop in blood pressure after injection of the intravenous gallbladder dye, observed both in experimental dogs and in human beings may account for the occurrence of shock noted in patients after injection of the dye. In patients with sclerotic arteries, the drop in blood pressure after intravenous injections of gallbladder dye

TABLE 2—*Readings of Blood Pressure Before and After Intravenous Injections of Iodophthalein Sodium*

Patient	Before Dye	Immediately	Five	Twenty Two
		After Dye	Hours After Dye	Hours After Dye
1 G B	94/64	88/60	106/80	110/70
2 F A	112/68	112/68	112/68	110/64
3 L S	121/86	112/78	100/76	110/78
4 J T	130/85	125/85	106/80	104/76
5 R M	136/86	120/82	138/90	124/81
6 M J	120/78	120/78	120/74	116/75
7	110/70	110/70	110/74	106/80

may produce enough diminution of coronary flow to result in coronary thrombosis.

4 While the mechanism of the production of coronary accidents by intravenous injections of gallbladder dye in persons with coronary arteriosclerosis is not fully explained by these experiments, it is clear that both blood pressure and coronary blood flow are profoundly affected. Obviously intravenous injections of gallbladder dye are contraindicated in persons with coronary arteriosclerosis.

# CHANGES IN THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH ENCEPHALITIS COMPLICATING PNEUMONIA

## I A CLINICAL STUDY

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In view of the extensive literature on the subject of pneumonia, it is surprising that the cerebral complications accompanying or following this disease have been almost entirely neglected. Three important factors probably account for the neglect of the subject of cerebral complications. 1 Pneumonia is usually treated by the internist, who in most cases is not greatly impressed by the milder cerebral symptoms. 2 The pulmonary involvement often overshadows and even covers many of the cerebral symptoms. 3 The great interest in the etiologic factors and the treatment of the pulmonary lesions has almost excluded any investigation of other phases of this illness. The existing literature on this subject, therefore, is comprised largely of isolated case reports published in French and South American journals. Bonaba and his associates,<sup>1</sup> in 1939, were able to collect from the literature but 28 cases of pneumonia encephalitis. Adler,<sup>2</sup> in reviewing 100 cases of postinfectious encephalitis occurring during a ten year period, observed 11 following pneumonia. The total cases of pneumonia during this same period numbered 18,000, making the percentage of cerebral complications but 0.06. When one considers that pneumonia is one of the most common diseases of the human race and that many patients with the disease are treated with but a minimum of medical care, it seems inevitable that many instances of mild or even severe encephalitis are being overlooked regularly and that the frequency of this complication is greater than is generally suspected. Detection of these complications becomes of paramount importance, since, as will be pointed out, severe

cerebral residuals may often follow relatively mild pneumonia.

Comby,<sup>3</sup> who first called attention to this most interesting complication, felt that this form of encephalitis is associated more often with bronchopneumonia than with lobar pneumonia. His contention has not been substantiated. As a matter of fact, encephalitis of a nonpurulent nature may follow almost every variety of pneumonia, even the more recently described "virus pneumonia" or virus pneumonia type A (Reimann).<sup>4</sup> The cause of these cerebral lesions is, as yet, unknown. Although most cases reported have occurred during infancy and early childhood, almost every age group may be involved. Generally, however, the nature of the cerebral complications is more dramatic in younger persons, and hence they attract more attention. Pneumonia encephalitis may appear at the beginning of, during or after the pneumonia, frequently appearing during convalescence, after the patient has become afebrile and appears well on the road to recovery. The onset of symptoms is usually abrupt but may be gradual and mild. There is a decided variability of symptoms, ranging from such generalized complaints as headache, vomiting, vertigo and lethargy to the more dramatic complications of coma, convulsions, delirium, monoplegia, hemiplegia, athetosis and psychic disturbances. The most common picture seen is that of an acute meningoencephalitis that appears either at the height of the illness or at the time the acute infectious process is subsiding (Bonaba and co-workers,<sup>5</sup> Reimann,<sup>4</sup> and de Filippi and Fernández<sup>6</sup>). The patient complains of head-

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1 Bonaba, J, Marcos, J R, and Mendivil de Agorio, S. Nuevos casos de encefalitis neumonica, Arch de pediat d Uruguay **12** 317, 1941.

2 Adler, A. One Hundred Cases of a Condition Diagnosed as Acute Encephalitis, Arch Neurol & Psychiat **44** 541 (Sept) 1940.

3 Comby, J. L'encephalite aigue chez les enfants, Arch de med d enf **10** 577, 1907.

4 Reimann, H A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filterable Virus, J A M A **111** 2377 (Dec 24) 1938.

5 Bonaba, J, Boni, E, and Barberouse, C M. Tres nuevos casos de encefalitis post-neumonica, Arch de pediat d Uruguay **8** 245, 1937.

6 de Filippi, F, and Fernandez, I. Encefalitis paraneumonica, Arch argent de pediat **11** 22, 1939.

ache, vertigo, vomiting, restlessness and some lethargy. In some cases the lethargy may deepen into coma, while in others the encephalitis may appear suddenly as deep somnolence in a patient who was apparently on the road to recovery (Bonaba and co-workers,<sup>5</sup> de Filippi and Fernández,<sup>6</sup> Nové-Josserand and associates<sup>7</sup> and Gareiso and Sageras<sup>8</sup>). Bonaba, Marcos and Mendivil de Agorio<sup>1</sup> reported 1 such case, that of a 5 year old child in whom the somnolence appeared before the onset of the pneumonitis. The child was extremely lethargic, revealed bilateral positive toe signs and signs of bilateral papilledema. This type of somnolence at times is associated with motor restlessness and extreme excitation.

In many instances, after a short period of generalized complaints, a severe delirium develops, with a clouded sensorium and even hallucinations (Mollard and Dufourt,<sup>9</sup> Reimann,<sup>4</sup> Eschbach,<sup>10</sup> Stephan,<sup>11</sup> Comby<sup>12</sup> and Navarro<sup>13</sup>). Since this development most frequently occurs during the height of the infectious process, it has been assumed to be due to the toxic state produced by the pyrexia. However, the appearance of a similar picture during convalescence (Navarro<sup>13</sup> and Mollard and Dufourt<sup>9</sup>), as well as the numerous associated neurologic observations, strongly suggest an independent encephalitic process. Mollard and Dufourt, for example, reported a case of a 44 year old man who, while recovering from grave pneumonia, suddenly experienced a severe delirium with overactivity, followed by lethargy, stupor, convulsions and death within a period of four days. In Eschbach's patient, the delirium appeared on the fourth day of illness and was accompanied with numerous focal symptoms, such as Kernig's sign, strabismus of the left eye and diplopia. Comby<sup>12</sup> reported the amazing case of a boy 4 years of age. Nine days after the onset of pneumonitis, the patient became delirious and experienced visual hallucinations.

After a few days a catatonic state manifested by generalized hypertonicity developed. Although the child seemed quiet and calm, his limbs would remain in peculiar positions, as in typical cataplexy. This patient was observed for only six weeks, but during that time he showed no signs of improvement.

Convulsions of both a focal and a generalized nature have been reported (Stephan,<sup>11</sup> Comby,<sup>12</sup> Eschbach<sup>10</sup> and Garzón<sup>14</sup>). Garzón's patient was a 2½ year old child, who was lethargic and had generalized seizures thirty-six hours after becoming afebrile. The spinal fluid revealed 120 cells, of which 84 per cent were mononuclear leukocytes. The child remained unresponsive, with a spasmodic rigidity of all limbs resembling a decerebrate rigidity. Death ensued in two weeks. Eschbach and Comby reported convulsions of a jacksonian type. In Comby's case, the convulsions were followed by persistent somnolence and paresis of the right side. Stephan studied a dramatic case in which generalized convulsions appeared at the height of the pneumonitis, accompanied with headaches, stiff neck and mild delirium. The convulsions continued for a week, leaving a spasticity of all limbs, particularly the lower, and ptosis and miosis of the right eye. Nine days after the onset of the cerebral involvement, the patient died in a state of respiratory paralysis.

Probably the most impressive of all the cerebral complications is the sudden onset of motor weakness occurring during convalescence and after the patient appears to be recovering (Mouriquand and associates,<sup>15</sup> Lesieur,<sup>16</sup> Regine,<sup>17</sup> Buchanan,<sup>18</sup> Barni,<sup>19</sup> Stephan,<sup>11</sup> Comby<sup>12</sup> and Eschbach<sup>10</sup>). Hemiplegias predominate, although monoplegias (Buchanan) and even quadriplegias (Comby) have been reported. Barni observed a 22 month old child in whom paralysis of the right side associated with aphasia appeared after four days of a normal temperature. Recovery began after nineteen days and was complete in one week. Regine's case was

7 Nové-Josserand, L., Rougier, and Feuillade. *Nevraxite consécutive à une pneumonie chez une enfant de 4 ans*. Guérison, *Lyon med* **153** 272, 1934.

8 Gareiso, A., and Sageras, P. O. *Encefalitis agudas en los procesos infecciosos*, *Rev argent de neurol y psiquiat* **2** 233, 1936.

9 Mollard, J., and Dufourt, A. *Sur l'encéphalite aigue au cours de la pneumonie*, *Lyon med* **66** 821, 1911.

10 Eschbach, H. *Pneumopathies à manifestations cérébro-méningées*, *Arch med-chir de Province* **27** 47, 1937.

11 Stephan, B. H. *Des paralysies pneumoniques*, *Rev de méd, Paris* **9** 60, 1889.

12 Comby, M. *Les encéphalitis aiguës post-infectieuses de l'enfance*, Thesis, Paris, Masson & Cie, 1935.

13 Navarro, J. C. *Neumonia, encefalitis, absceso de fochier*, *Prensa med argent* **7** 409, 1932.

14 Garzón, W. P. *Meningoencefalitis postneumonica*, *Med de los niños* **35** 261, 1934.

15 Mouriquand, G., Bernheim, M., and Boucomont, J. *L'encéphalite aigue dans la pneumonie infantile*, *Presse méd* **41** 211, 1933.

16 Lesieur, M. M., Froment, J., and Garin, C. *Hémiplégie pneumonique et pneumococcie méningée sans réaction leucocytaire du liquide céphalo-rachidien*, *Bull et mem Soc méd d hôp de Paris* **28** 570, 1909.

17 Regine, A. *Encefalo-mielite nella bronco-polmonite infantile*, *Riforma med* **50** 667, 1934.

18 Buchanan, D. N. *Repeated Attacks of Hemiplegia with Ataxia and Bulbar Palsy in a Child*, *Proc Roy Soc Med* **24** 1064, 1930.

19 Barni, B. *Sindrome encefalitica transitoria postneumonica*, *Riv sper di freniat* **12** 31, 934, 1935.

much more dramatic and less favorable. His patient was a 6 year old child, in whom weakness of the right arm and both legs developed after five days of convalescence. Neurologic examination revealed right strabismus and weakness of the right arm with spastic paraplegia of the lower limbs. The patient improved slowly but after forty days suddenly had a recurrence of the pneumonia and died in a state of extreme psychomotor excitement. Buchanan reported neurologic complications persisting over a four year period, indicating a continued action of the pathologic process. At the onset his patient was unconscious for three weeks. After recovery she was blind and dragged her left leg. Periodically during the next four years, this patient had varying neurologic disabilities, which improved only to recur. These consisted of drowsiness, vomiting, tremor of hands, facial weakness and varying monoplegias and hemiplegias. At the time she was last seen, she still revealed a persistent hemiplegia of the right side, with gross ataxia of both arms.

In addition to these more common complications, isolated reports are available indicating a fairly widespread and unpredictable localization of the cerebral pathologic process, producing amauroses (Buchanan<sup>18</sup>), aphasias (Prandi,<sup>20</sup> Bonaba and Cantonnet<sup>21</sup> and Carrau<sup>22</sup>), conjugate deviations (Prandi<sup>20</sup>) and varying types of involvement of the extrapyramidal system (Gareiso and Sagieras,<sup>8</sup> Bernheim and Bonnefoy<sup>23</sup> and Moniquand and associates<sup>15</sup>).

In view of the paucity of reports on this most striking and often most important complication of pneumonia, it was felt that a review of some of our cases might serve the purpose of stimulating more interest in this form of cerebral pneumonia. The possibility of such persistent cerebral complications even in the face of mild pneumonitis makes it imperative that the presence of any involvement of the central nervous system be considered in the ultimate prognosis of any case of pneumonia, particularly when the disease occurs in a child. In selecting our cases we have attempted to use those which demonstrate the various clinical varieties of cerebral involvement.

<sup>20</sup> Prandi, G. Di quattro casi di afasia insorti durante malattie infettive, *Pediatrica e med prat* **10** 240, 1935.

<sup>21</sup> Bonaba, J., and Cantonnet, H. Neumococias extrapulmonares de la infancia, *Arch de pediat d Uruguay* **9** 396, 1935.

<sup>22</sup> Carrau, A., cited by Bonaba, J., and Barberouse, Diag M. Encefalitis postpneumonica en al niño, *An Fac scycle med de Montevideo* **24** 28, 1939.

<sup>23</sup> Bernheim and Bonnefoy. Encephalite aigue au cours d'une pneumonie infantile, *Lyon med* **152** 335, 1933.

## REPORT OF CASES

CASE 1—N. K., a 10 year old girl, was first taken ill with a mild cough and a slightly elevated temperature. During the next few days her temperature rose to 104 F., and she was hospitalized. Examination revealed rales and scattered areas of dullness in the left side of the chest. Roentgenograms of the lungs showed a peribronchial infiltration in the subclavicular region. Roentgenographic examination four days later showed the process to have extended. The patient continued to be septic for six days, with temperatures ranging from 99 F. to 105 F. No organisms could be cultivated from the sputum, and there was no response to chemotherapy. After six days her temperature gradually returned to normal, and convalescence ensued. Throughout her entire illness the patient remained mentally clear and cooperative.

On the sixth day of convalescence the patient suddenly vomited and became unresponsive. When she did talk, her speech was slurred, and she appeared confused and bewildered. Three days later she began to respond slightly by shaking her head. Throughout this time her temperature remained normal, and she did not appear toxic. Examination three days after the onset of the cerebral symptoms revealed her fundi to be slightly congested. There was a weakness of the right upper and of the left lower extremities, with hyperactive reflexes in the paretic limbs. There was a positive toe sign on the left. Coordination was poor in the left lower limb. All sensation was intact. A spinal puncture showed 20 cells per cubic millimeter, with 90 per cent mononuclear leukocytes.

Improvement continued to be slow. The patient became more alert, and her slurred speech disappeared. She had only a vague recollection of some of the occurrences during her acute illness. After six weeks of convalescence, she was allowed to be up but noticed great difficulty with gait. Neurologic check-up at this time revealed persistent signs. She had difficulty repeating test phrases. She seemed somewhat unstable emotionally, giggling readily and without provocation. There was weakness of the right upper and both lower limbs. The right triceps reflex was greater than the left, while the left ankle and knee jerks were greater than the right. There was a bilateral ankle clonus. The Romberg sign was elicited, and there was a definite ataxic gait. Psychometric examination revealed definite evidence of organic deterioration of the brain. This patient was again examined three months after the acute illness. Her neurologic signs had remained unchanged, except that her ataxia had become somewhat improved. Her gait was unsteady and incoordinated. Psychometric testing still showed evidence of organic deterioration.

*Comment*—This case is of extreme significance, since it indicates how dramatically severe complications affecting the nervous system may appear in association with relatively mild and subsiding pneumonia. In this patient, unfortunately, the cerebral damage appears to have been irreversible, so that three months after its onset definite and incapacitating residuals still remained.

CASE 2—B. R. was a 1 month old girl, in whom four days prior to her hospitalization pneumonia associated with thrush of the nose and throat developed. Her chief symptoms consisted of cough, fever and bubbling rales and rhonchi audible over both lungs. The leuko-

cyte count was normal. Roentgenograms of the chest revealed a pneumonic process. Cultures of materials from the nose and throat failed to disclose a causative organism.

After the first week, the infant's temperature remained normal for three days but thereafter had an intermittent course, usually rising no higher than 102 F to 103 F. Her cough continued. A mild cyanosis and respiratory difficulty occasionally required administration of oxygen. She soon became lethargic and drowsy and would often fall asleep, even while being attended by the nursing staff. At times the somnolence was pronounced, but the patient could still be aroused. It was also noted that she remained listless and apathetic and even remained asleep during intermittent periods of respiratory distress. The infant's condition became steadily worse, and she died on the twentieth day of her illness.

*Autopsy*—There were patchy bronchopneumonia and a multiplicity of small abscesses throughout both lungs. The external surface of the brain showed no discernible abnormalities. On coronal section, a large number of small petechial hemorrhages were observed throughout the subcortical white substance of both cerebral hemispheres. Definite petechiae were not found in either the brain stem or the cerebellum.

Microscopic studies of the brain demonstrated an extremely severe vascular congestion throughout all regions, associated with a prodigious number of petechiae in the cerebral white matter. The petechiae were usually of the ring variety, but ball hemorrhages were not uncommon. Occasionally a capillary was occluded by a typical platelet thrombus. The nerve cells in many regions of the cortex exhibited chromatolysis and swelling.

**CASE 3**—Baby H was a boy born two months prematurely. Since the mother had mild preeclampsia, labor was induced, and delivery occurred without any complication. The child was entirely normal and suffered from no respiratory distress. The Wassermann reaction of the cord was negative. The mother had always been in good health and had one older child, who was living and well.

Examination of the infant revealed no abnormality other than prematurity. His condition progressed favorably for twenty-five days. On the twenty-sixth day, labored and irregular respiration, cough, a low grade fever and leukocytosis developed. Numerous rales were heard bilaterally over the lungs. Roentgenograms of the chest revealed a pneumonic involvement of the upper lobes of both lungs.

The patient's condition improved slowly. The entire course was relatively afebrile, with only occasional elevations of temperature between 100 F and 101 F. After a period of improvement for fourteen days, the infant became noticeably nervous and apprehensive and frequently refused his feedings. Any disturbance caused a generalized shaking suggestive of convulsive movements. A roentgenogram of the chest four days later demonstrated that considerable resolution had taken place, the left lung being entirely clear. Another roentgenogram of the chest six days later showed only a minimal residual of the consolidation in the upper lobe of the right lung. In spite of this improvement of the pneumonic process, the patient remained irritable and restless. Two weeks after the onset of the neurologic complications and a month after the beginning of the pneumonia, a positive Chvostek sign was noted. Tetany was excluded by a blood calcium value of 11.3 mg per hundred cubic centimeters. The infant became weak, had an intermittent low grade fever and manifested a generalized trembling of the entire body. Two days

later he suddenly lost consciousness, his eyes deviated upward, and he vomited. After this he remained listless, and dysphagia developed. Thereafter he failed rapidly, and he died later that day.

A spinal puncture was performed immediately after death. It revealed a pleocytosis of 189 cells per cubic millimeter, almost all of which were mononuclear leukocytes. The protein content of the spinal fluid was also elevated, being 126 mg per hundred cubic centimeters.

*Autopsy*—There was a congestion of the lower lobes of both lungs. Microscopic study of the lungs demonstrated only mild bronchopneumonia showing resolution. Both the liver and the spleen were slightly enlarged apparently as a result of chronic congestion. The external examination of the brain showed nothing abnormal.

Microscopic studies of the brain revealed a prominent vascular congestion and an occasional petechial hemorrhage. A few of the larger hemorrhages were rather diffuse. In a few vessels there was a sparse leukocytic infiltration of the adventitia, consisting of a small number of either mononuclear leukocytes or neutrophils or of an admixture of both. A similar sparse exudate was also observed in the leptomeninges in scattered small areas. This was generally associated with a well defined vascular congestion and small extravasations of blood. Nerve cell disease was present in the cortex and consisted mainly of irregular areas of neuronal shrinkage and pyknosis. The Purkinje cells of the cerebellum were swollen and chromatolytic.

*Comment*—This illustrates a typical instance of death due to a cerebral complication in the course of a recovering pneumonic process. In spite of the mild course of the original pneumonia and in the absence of severe pyrexia, this patient had cerebral symptoms indicative of a widespread cerebral involvement. The severity of the encephalitis was not influenced by the extent of the precipitating pulmonary involvement, and, as is occasionally the case, the illness terminated fatally after a fairly rapid downhill course.

**CASE 4**—E. A., a 45 year old woman, first showed evidence of a pneumonic process two days before her admission to the hospital. She seemed to be progressing fairly well until shortly before her admission, when she suddenly became comatose without exhibiting any other associated symptoms. Examination revealed the patient to be entirely unresponsive. Her pupils were pinpoint-sized and fixed. There were many fine and coarse rales throughout both pulmonary fields. The patient showed no evidence of any motor weakness but did have bilateral positive toe signs. The patellar reflexes were reduced. The Brudzinski sign was slightly positive, but Kernig's sign was not elicited. Examination of the sputum showed a type VIII pneumococcus.

The patient's temperature during the next few days ranged between 99 F and 101 F. Shortly after her admission a lumbar puncture was performed, and, while the fluid was clear, there was noticeably increased pressure. The patient continued to remain unresponsive and involuntary. Twitchings of her arms and legs developed, and she died after three days of coma.

*Autopsy*—There was a pneumonic consolidation of the middle and upper lobes of the right lung, as well as a number of smaller areas of patchy consolidation within the left lung. The external surface of the brain appeared essentially normal. Coronal sections however

demonstrated a large number of petechial hemorrhages disseminated throughout the subcortical white matter and basal nuclei of both cerebral hemispheres. A smaller number of petechiae were scattered throughout the cerebellum. The pons and medulla appeared normal.

**CASE 5—E C**, a 50 year old man, was admitted to the hospital with lobar pneumonia. Shortly after the onset of his illness the patient, who had been in good health, had a grave delirium with extreme psychomotor overactivity. His mental involvement necessitated his transfer to the hospital.

At the time of his admission he was found to be acutely ill, with a temperature of 103 F, rapid respiration and slight cyanosis. Although he appeared lethargic, he was extremely restless. He was poorly oriented and at times confused. On the third day of his stay in the hospital he showed evidence of early bilateral papilledema. His temperature rose to 105 F, and he became more irrational. He became extremely restless and at times agitated, wandering from his bed and being very difficult to control. Because of his motor overactivity, restraints were required to keep him in place. He continued to manifest an extreme delirium, failing rapidly and dying on his fourth day in the hospital.

Although early cultures of the blood showed no growth, a postmortem culture yielded a nonhemolytic *Streptococcus*.

**Autopsy**—The lungs showed an extensive lobar pneumonia in the stage of early resolution. Gross examination of the brain displayed a vascular congestion.

Microscopic sections revealed pronounced vascular congestion and scattered petechiae in the form of small perivascular extravasations and ball hemorrhages. In a few regions, small amounts of blood had escaped into the subarachnoid space. The neurons of the cerebral cortex and those of the nuclei of the cranial nerves showed regressive alterations. While many nerve cells were shrunken and pyknotic, others had undergone swelling and tigrolysis with a few ghost cells resulting. In irregular focal areas the myelin displayed a minimal loss of its tinctorial properties.

**Comment**—This case represents an instance of fulminating pneumonia during which the patient showed severe delirium. Although the cerebral complications in this case could be ascribed to the toxic effects of the pyrexia, it is interesting to note that the cerebral changes were similar to those seen in cases in which no severe toxicity appeared to be present. It is also of interest to note that in this case of apparent streptococcic pneumonia the cerebral changes were similar to those seen in the previously reported cases of pneumococcic and virus pneumonia.

**CASE 6—N P** was a white man 29 years of age, whose illness began six days before his hospitalization. His early complaints consisted of a nonproductive cough, fever, general malaise and diffuse discomfort in the joints and muscles. On the fifth day of his illness generalized asthenia, severe coughing, excessive sweating, slight lethargy, irritability and a temperature of 104 F developed.

Examination at the time of his admission revealed diminished breath sounds over the lower lobes of both lungs and a strong suggestion of audible bronchial breathing over the lower portion of the left lung.

Mild tympanitis and epigastric tenderness were noted. Although the patient's sensorium seemed to be somewhat clouded, he was able to converse coherently without a sign of confusion. Roentgenograms of the chest demonstrated a bilateral patchy involvement typical of lobular pneumonia.

In spite of moderately large doses of sulfathiazole, the patient remained acutely ill for seven days. On the eighth day his temperature dropped to 99.4 F, and his general condition improved considerably. It appeared as if his recovery had begun. However, within the next twenty-four hours he rather abruptly became stuporous, and complete hemiplegia of the right side with concomitant motor aphasia developed. There also appeared episodes of twitching of the upper and lower limbs on the left, which recurred intermittently at varying intervals for the next few days. A lumbar puncture yielded a clear spinal fluid, which contained a slight increase in protein (59 mg per hundred cubic centimeters) with no increase in cells.

During the ensuing days his condition steadily improved. His sensorium gradually cleared, but he remained noticeably lethargic. At times he would be restless and irritable, showing evidence of explosive anger. Motor function gradually began to return in his lower limb, but there was no recovery in his upper extremity. His speech also improved, so that after a period of two months most of his conversation could be understood. Even at this time, if the patient became tired or excited, his speech would again become unintelligible. His strength continued to improve, so that at the time of his discharge, two months after the onset of the cerebral complications, he was able to walk unassisted but with a definite limp.

Improvement continued after he left the hospital. One year later, however, he still showed a definite defect of gait and was unable to write with his right hand. He still complained of occasional difficulty in finding the correct words to express himself. His irritability persisted and at times resulted in definite outbursts of temper. He was last examined one and one-half years after his acute illness. He still presented evidence of a mild disturbance of the personality and of slight intellectual deterioration. There were a minimal paresis of the right lower side of the face and a mild weakness of the grip in the right hand. The lower limbs revealed no involvement, although an ankle clonus was elicited on the right. The patient's pronunciation of words was not disturbed, however, he showed considerable difficulty in expressing his thoughts.

**Comment**—The sudden onset of the hemiplegia in this case would naturally suggest the possibility of the occurrence of some embolic process. However, when one reviews the observations more carefully, it readily becomes apparent that the involvement was much more widespread and that the hemiplegia was only a single expression of a widely disseminated encephalitic process.

#### RESUMÉ OF CLINICAL OBSERVATIONS

The clinical picture produced by the involvement of the central nervous system in pneumonia is characterized by a noticeable variability from case to case. Judging from a review of the cases reported in the literature as well as from our own studies, we can divide the clinical syn-

diomes generally seen into five relatively independent groups. These divisions are of definite importance, since each seems to carry with it certain characteristics which are of both diagnostic and prognostic significance. Each group, therefore, warrants a brief comment.

1 *Generalized Symptoms of a Nonspecific Nature* (case 1) —The symptoms in this form of the illness are of a general nature and consist of headache, vomiting, diplopia and mild lethargy often interrupted by periods of excitement. These complaints generally appear shortly after the onset of the pulmonary symptoms and disappear after the pneumonic involvement recedes. At times these symptoms may become severe, developing into fairly intense lethargy or severe excitement, or even visual hallucinations. The neurologic examination will reveal scattered signs. Signs of meningeal irritation almost invariably occur during the first few days of the illness, only to be the first of the cerebral symptoms to disappear. The prognosis in this form of illness is generally good. In most cases recovery is complete within two weeks, with no residuals. In only 1 case reported by Reimann<sup>4</sup> was death due to the encephalitic involvement. The changes in the spinal fluid vary from none to a pleocytosis of as high as 270 cells (Reimann). As a rule there is a mild pleocytosis, consisting chiefly of mononuclear leukocytes.

2 *Delirious Form* (case 5) —Often during the height of the pneumonia there is an acute delirium. The onset most often is gradual, the patients becoming apprehensive, restless, bewildered and mildly confused. They may be quiet and muttering or may show a severe psychomotor acceleration with overactivity, visual hallucinations and even occasional catatonic states (Comby<sup>12</sup>). In Navarro's<sup>13</sup> case, the delirium passed into a deep stupor. Neurologically, these patients may show scattered signs, although some are entirely normal. The spinal fluid reveals a pleocytosis in about half the cases. Recovery is the rule and occurs rapidly after a few days of confusion. In some, however, the mental complication may persist for weeks or even months. Comby reported 1 such case, in which the psychotic state persisted as a permanent residual.

3 *Convulsive Type* (case 3) —It is questionable whether this type constitutes a separate form of complications of the central nervous system associated with pneumonia or whether it merely comprises an accompanying symptom of the other forms of cerebral complication. In most of the reported cases, the convulsions oc-

curred independently of any other manifestations and hence have been placed by us as a separate group. The convulsions are usually generalized and appear from four to fifteen days after the pneumonia. Occasionally the convulsions may be focal, resembling a typical jacksonian seizure. They are usually recurrent over a period of days and are followed by periods of lethargy or somnolence. The prognosis is invariably favorable in this type of case, improvement beginning within a few days. Complete recovery, however, is usually delayed, requiring from one to three months. In the occasional case, as the convulsions disappear, residual complications become apparent in the form of paresis of the various limbs (Comby<sup>12</sup> and Stephan<sup>11</sup>). Results of examination of the spinal fluid have been reported in only a few of these cases and in all have been normal.

In the three types of cerebral complication just described, the symptoms appear at the height of the pneumonia and have, therefore, been suspected of resulting from a toxic condition due to the high temperature. Although this suspicion may be warranted in some cases, the occurrence of similar neuropsychiatric syndromes during convalescence and after the temperature has been normal for days, the delayed recovery, the occasional increased cell count of the spinal fluid and the permanent residuals certainly suggest some additional causative factors besides the pyrexia.

4 *Lethargic Type* (cases 2 and 4) —This is by far the most unpredictable form of complication and occurs with equal frequency during the height of the illness and during convalescence, when the patient seems to be recovering. The onset is always dramatic and abrupt, with the patient suddenly becoming unresponsive and stuporous within a period of minutes or hours. This lethargic or stuporous state lasts for hours, days or even weeks and then almost invariably begins to recede slowly, requiring many weeks for complete recovery. As the lethargy disappears and the patient becomes more responsive, scattered associated disturbances become apparent. Many patients reveal motor aphasia or scattered motor weaknesses that persist for weeks or months. Recovery, although delayed, is the rule. The spinal fluid is usually normal, even though in 1 case of Garzón<sup>14</sup> there were 120 cells, of which 84 per cent were mononuclear leukocytes.

5 *Hemiplegic Form* (case 6) —This form of complication no doubt comprises the most spectacular of the symptoms and emphasizes the importance of caution in evaluating the prognosis even after mild pneumonia. The onset

is usually sudden and occurs from a few days to a few weeks after the patient's temperature has returned to normal and during a period when recovery would seem inevitable. The severity of the pneumonic process plays no part in the incidence of this complication, since it may be seen in patients in whom the original pneumonia was mild. The motor involvement may be complete or partial or may involve one or more limbs. It usually consists of a severe hemiparesis. There is no predilection for any particular side of the body. In a few cases the motor weakness is not noticed until the patient attempts to walk after a prolonged period of rest in bed. The cell count of the spinal fluid is usually normal, although a pleocytosis has been reported (Grenet and associates<sup>24</sup>). Recovery is delayed and begins in about two weeks. Improvement is slow, requiring months or years for complete recovery. In about half the cases, residual weakness can be expected. Buchanan<sup>18</sup> reported 1 case in which recurrent weaknesses occurred over a period of four years, with resultant right hemiplegia and ataxia.

#### COMMENT

Probably one of the most puzzling problems concerning the involvement of the central nervous system in pneumonia is that regarding the actual nature and cause of such complications. In attempting to arrive at any etiologic interpretation, one must keep in mind certain definite clinical facts, all of which tend to point to a common factor in most cases. Pneumonia, as is well known, can be caused by numerous different organisms, such as *Streptococcus* (Miller and Lusk<sup>25</sup> and Small<sup>26</sup>), *Staphylococcus* (Chickering and Park,<sup>27</sup> Reimann<sup>28</sup> and Baker<sup>29</sup>), *Pneumococcus*, influenza bacillus (Goodpasture and Burnett<sup>30</sup> and Hall, Stone

and Simpson<sup>31</sup>) and viruses (Kneeland and Smetana<sup>32</sup> and Reimann<sup>4</sup>). In each type of pneumonia cerebral complications of a similar clinical and pathologic nature may occur. This variation immediately speaks against the etiologic organism of the pneumonia as the probable agent causing the encephalitis. It would be almost impossible for such a wide variety of different organisms to invade the brain through a similar hematogenous route and produce similar pathologic lesions. These facts narrow the etiologic field down to three remaining considerations.

1 *Toxic Theory*—It is well known that scattered cerebral symptoms may occur as symptoms of toxemia secondary to pyrexia in any illness. This is particularly true in children in whom vomiting, headaches, apathy and convulsions are extremely frequent. However the occurrence of such symptoms following a mild pneumonic process and often after the pneumonia has subsided forces one to speculate on the presence of some other toxin, one not necessarily associated with the pyrexia but more directly related to the pneumonia and to the individual susceptibility to cerebral involvement.

2 *Virus Theory*—A second theory would involve the activation by the pneumonia of some unknown virus which already was present in the brain. At present there is no proof for or against such a theory. Certainly the consistency of the clinicopathologic picture in spite of the wide variety of pathologic organisms involved in the pneumonia would tend to favor such a theory.

3 *Allergic Theory*—Recently Ferraro<sup>33</sup> advocated an allergic reaction of the brain as the cause of the cerebral symptoms in postscarlatinal encephalitis. He assumed that an allergic phenomenon took place in the central nervous system during the infectious disease. Certainly in favor of this theory is the similarity of the pathologic lesions in our cases with those described by Ferraro as occurring in acute allergic reactions. The acceptability of this theory will be discussed in more detail in a later publication.

Finally it seems imperative to emphasize again the significance of these changes in the

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25 Miller, J. L., and Lusk, F. B. Epidemic of *Streptococcus* Pneumonia and Empyema at Camp Dodge, Iowa, *J A M A* **71** 702 (Aug 3) 1918.

26 Small, A. A. Pneumonia at a Base Hospital. Observations in One Thousand and One Hundred Cases at Camp Pike, Ark., *J A M A* **71** 700 (Aug 31) 1918.

27 Chickering, H. T., and Park, J. H., Jr. *Staphylococcus Aureus* Pneumonia, *J A M A* **72** 617 (March 1) 1919.

28 Reimann, H. A. Primary *Staphylococcic* Pneumonia, *J A M A* **101** 514 (Aug 12) 1933.

29 Baker, R. D. *Staphylococcal* Pneumonia During Epidemic Influenza in North Carolina (1941), *South M J* **35** 240, 1942.

30 Goodpasture, E. W., and Burnett, F. L. The Pathology of Pneumonia Accompanying Influenza, *U S Nav M Bull* **13** 177, 1919.

31 Hall, J. N., Stone, M. C., and Simpson, J. C. The Epidemic of Pneumonia Following Influenza at Camp Logan, Texas, *J A M A* **71** 1986 (Dec 14) 1918.

32 Kneeland, Y., and Smetana, H. F. Current Bronchopneumonia of Unusual Character and Undetermined Origin, *Bull Johns Hopkins Hosp* **67** 229, 1940.

33 Ferraro, A. Allergic Brain Changes in Postscarlatinal Encephalitis, *J Neuropath & Exper Neurol* **3** 239, 1944.

central nervous system. In many cases, as exemplified by our cases 1 and 3, cerebral complications of a most severe degree followed relatively mild pneumonia. Such cases emphasize the importance of a careful neuropsychiatric examination of every patient ill with pneumonia to determine the presence of such cerebral symptoms. Any indication of involvement of the central nervous system should be an absolute indication for more prolonged care, with extreme caution in any prognostic evaluation offered. The favorable course of the pneumonia does not necessarily mean that recovery will be complete and uncomplicated. This study also suggests that many instances of mild cerebral involvement after pneumonia are probably being overlooked regularly. Such cases may be the etiologic basis of so-called unknown neuropsychiatric sequelae that are observed from time to time in children.

## SUMMARY

Pneumonia, regardless of the causative organism, may be complicated by an involvement of the central nervous system.

The severity and frequency of the resulting encephalitis do not correlate with the severity of the pulmonary involvement. Relatively mild pneumonia may be followed by severe cerebral damage.

The clinical pictures produced by the involvement of the central nervous system can be divided into five groups, each showing certain definite clinical characteristics which may be of both diagnostic and prognostic significance. These groups are as follows: (1) that characterized by generalized symptoms of a nonspecific nature (headache, vomiting, lethargy and irritability), (2) delirious type, (3) convulsive type, (4) lethargic type, and (5) hemiplegic type.

# PUTRID PULMONARY ABSCESS WITHOUT FOUL SPUTUM (SHUT-OFF PULMONARY ABSCESS)

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During the past sixteen years, the pathogenesis, clinical manifestations, prognosis, complications and therapy of putrid pulmonary abscess have been discussed in detail by the group concerned with thoracic diseases at Mount Sinai Hospital. The clinical picture of acute putrid pulmonary abscess developed by these studies and publications differed in a number of respects from the accepted one. This difference was particularly striking regarding therapy, for it was learned that relatively early surgical unroofing of the abscess effected a rapid cure, prevented the appearance of complications and forestalled the development of bronchial distortions and fibrotic pulmonary changes. The validity of this departure from the previously accepted therapy has been amply proved by the results. Operative drainage of acute putrid pulmonary abscess is becoming accepted as the correct therapeutic approach.

An experience with several hundred cases of acute putrid pulmonary abscess not only has provided an understanding of the more typical or classic cases but also has revealed numerous variations. In most instances the diagnosis of acute pulmonary abscess is made easily. About one week after extraction of a tooth or tonsillectomy or often without any preceding unusual event, localized thoracic pain, cough and hemoptysis develop. The expectoration of foul sputum completes the picture. Roentgenologic examination of the chest reveals a circumscribed area of density or a pulmonary excavation up to several inches in diameter. A fluid level is often present. There are many variations of the clinical picture in relation to time of onset, character of cough or amount of sputum. In general, however, these variations do not make for difficulties in diagnosis. There are atypical roentgenologic features which may lead to errors in interpretation concerning the progress of the disease but not concerning the diagnosis in the presence of foul sputum.

There is, however, a not inconsiderable group of cases in which the foulness of the sputum

either is absent or appears late, and these cases offer difficulties in diagnosis. Even with a great awareness of the disease on the part of the diagnostician, there were instances in which the diagnosis was long delayed or was not made. In recent years persistence in certain efforts, to which reference will be made, usually has provided the diagnosis. However, we may refer at once to a recent case of putrid pulmonary abscess in which the diagnosis was not made during several weeks of observation in the hospital despite such efforts, although it was strongly suspected throughout the period of observation. Prolonged delay in diagnosis may lead not only to increased morbidity and complications but also to death from spread of the disease beyond the limits of operative relief. Thus the necessity of establishing the diagnosis is of clinical importance and warrants full discussion.

The cases to be considered in this paper are instances of acute putrid pulmonary abscess without foul sputum. We have termed this variety "shut-off abscess" on the assumption that the bronchus communicating with the abscess is occluded as a result of an inflammatory reaction and cannot drain the contents of the abscess. In some instances a shut-off pulmonary abscess may go on to a putrid empyema, creating a special problem in diagnosis and therapy. The subject of putrid empyema without foul sputum (which we have termed "surprise" putrid empyema) will be discussed elsewhere.

The sole distinctive feature of a putrid pulmonary abscess is the foul or fetid odor. There are other clinical features which will often offer diagnostic leads, but it is on the odor of the sputum that the most reliance must be placed. When this odor is absent, the likelihood is great, but not absolute, as we shall show, that the pulmonary lesion is not of this nature. Therapy is based largely on the presence or absence of foul sputum. However, foul and gangrenous acute or subacute pulmonary abscesses may exist for months or longer in exceptional instances without foul sputum or foul breath.

The foulness of the sputum in connection with pulmonary abscess obviously depends on the

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From the medical services and the surgical service of Dr. Harold Neuhof, Mount Sinai Hospital.

patency between the seat of the disease and the draining bronchi. An odor will not be present if bronchial edema and secretion effectively seal the bronchial lumen from the abscess proper. There is no reason to believe that the abscess differs in any other respect from the typical putrid abscess. It can be said with reasonable assurance that most, if not all, putrid pulmonary abscesses are shut off to some extent. Thus a characteristic feature is the bronchoscopic finding of edema of the bronchus leading to the abscess. Another feature to be noted in many cases is that the sputum, after being at first foul and expectorated in large quantities, is thereafter only intermittently foul, in other cases there is no history of foul sputum after the initial episode. The difficulty in visualizing the cavity by the introduction of radiopaque fluid is well known. Although the diagnosis is much more readily made when the abscess is only partially shut off, there is no discernible difference in the pathologic characteristics of the two varieties. In both, the abscess is usually of substantial proportions, situated superficially within the lung with overlying visceroparietal adhesions. However, in the truly shut-off abscess a far greater tendency toward invasion of the pleura can be anticipated, the possibility always exists of late perforation of the shut-off abscess into the bronchial tree. The question of the existence of smaller abscesses ("cortical") from which foul sputum is never derived and which are presumed to be sources of putrid empyema is a separate one which will be discussed elsewhere under the title "Putrid Empyema Without Foul Sputum."

The discussions of a decade ago concerning the pathogenesis of the various types of pulmonary abscess have ceased for the most part in recent years. Almost all observers now believe that putrid pulmonary abscess is due to aspiration of infected material, which is assumed to lodge in a sublobar bronchus, producing a severe acute necrotizing inflammation, edema and at least partial occlusion of the lumen. The bacteria contained within the bronchus multiply and spread to the neighboring blood vessels and lymphatics, causing vascular thrombosis. At the same time, they infiltrate the segment of lung (bronchopulmonary segment) supplied by the more or less occluded bronchus, producing necrosis and a gangrenous inflammatory process. From the beginning a putrid pulmonary abscess includes a bronchial lesion, and fair-sized bronchi are involved. The appearance of foul sputum, usually within two weeks of the inception of the lesion, is evidence that the abscess which has formed either has drained through the com-

municating bronchus, the edema of which has subsided, or has perforated into the bronchus. In no more than 5 per cent of our cases was such drainage lacking, but this percentage represents the group in which the diagnosis of putrid pulmonary abscess was difficult. There is no obvious explanation for the shut-off type. At operation the appearance of the abscess cavity with its communicating bronchial orifices is identical with that of other abscesses. One can only assume that the persistence of occlusion of the communicating bronchus is caused by edema and lodgment of detritus.

The observation of putrid pulmonary abscess without foul sputum is not new, although this series appears to be the first of such cases to be gathered and studied. Lord<sup>1</sup> in 1919 mentioned that "in very rare instances the sputum and the breath are not malodorous and the absence of the bad odor is, therefore, not an assurance against abscess." Wessler and Jaches<sup>2</sup> noted the rupture of "cortical pulmonary abscesses into the pleural cavity as a cause of putrid empyema. Eggers<sup>3</sup> suggested the presence of similar occurrences in his case reports (cases 2, 3 and 5). Neuhof and Wessler<sup>4</sup> in 1932 offered the first distinctive description of such cases, stating that "the expectoration of foul pus does not occur in the small cortical type of lung abscess and in exceptional cases of shut-off abscesses." The point was reiterated by Neuhof and Hirshfeld<sup>5</sup> and Touroff and Moolten<sup>6</sup> several years later.

The cause of shut-off pulmonary abscesses apparently is the same as that of other acute putrid abscesses. In a study<sup>7</sup> dealing with the etiology and the pathogenesis of acute putrid pulmonary abscess, it was pointed out that an obvious cause was not present in 64 per cent of 115 cases. In these, a large percentage of the patients had significant gingivodental infections. It was hypothesized that abscesses of obvious cause resulted from aspiration of infective matter

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5 Neuhof, H., and Hirshfeld, S. *Ann. Surg.* **100**:1105, 1934.

6 Touroff, A. S. W., and Moolten, S. E. *J. Thoracic Surg.* **4**:559, 1935.

7 Stern, L. *J. Thoracic Surg.* **6**:202, 1937.

into small bronchi. The usual etiologic factors were general anesthesia, extraction of a tooth, coma and tonsillectomy or other operative procedures within the mouth, nose or pharynx. In cases without such factors, it was felt that anaerobically infected material from the gums and teeth had been aspirated during sleep or possibly at other times. In the series of shut-off abscesses presented here, the etiologic factors were similar. One patient had a tooth extracted three weeks before the onset of the disease, and another underwent a thyroidectomy under general anesthesia. In the remaining cases, there was no obvious cause, but most of the patients had grossly diseased teeth or gums or excess tartar.

The clinical picture of the shut-off type of pulmonary abscess depends on the size of the pulmonary lesion, its position, the imminence of or the actual existence of perforation into the pleural space, the extent of the pleural infection and the presence of unrelated pulmonary or other disease. If the pulmonary lesion is of substantial size, the main symptoms are likely to be cough and expectoration. These vary, however. In 1 case, there was as much as 14 ounces (420 cc) of non-foul sputum daily, while in another the sputum was scant. In some instances, a gangrenous pulmonary abscess is so well tolerated locally, and occasionally systemically, that the symptoms are insignificant. Cough may be slight or in rare instances completely lacking. It may be of a persisting hacking nature, accompanied with sputum at times, and may be productive of blood. Not only its severity but also its frequency may vary greatly. The cough may disappear for intervals and then recur. Bizarre courses have been observed. The relative mildness of cough and expectoration in the presence of a substantial pulmonary lesion may be a striking feature of the shut-off abscess.

Either the presence or the absence of a pronounced constitutional response, such as a high level of leukocytes and fever, may be disproportionate to the size of the abscess. The clinical picture often is alarming when the lesion has spread to the pleura with extensive putrid pleural infection. To this there may be added respiratory embarrassment if there is displacement of or pressure on mediastinal structures.

Pain is a general guide to the position of the lesion. Most putrid pulmonary abscesses are accompanied in some stage of their development (usually at the onset) with pains in the chest, often severe. The area of pain usually points to the site of pleuritis. When in rare cases the lesion faces an interlobar fissure, the diaphragm or the mediastinum, the location of the pain may

be at variance with the situation of the abscess or pain may be absent. The importance of the appreciation of the significance of pains in the chest is greater in putrid pulmonary abscess than in many other forms of pulmonary disease. Pains in the chest almost always mean pleural involvement. In all cases, with rare exceptions, productive pleuritis seals the visceral and parietal pleurae over the lesion. The acute inflammatory element usually subsides in a short time, and with its subsidence the pain often disappears. Recurrence or persistence of severe pain indicates further pleural involvement, it strongly suggests an extension of the gangrenous pulmonary lesion toward the pleural surface and possibly an imminent empyema.

The factors responsible for spread to the pleura are not entirely known. In certain otherwise typical cases of uncomplicated putrid pulmonary abscess, sudden or gradual extension of the lesion to the pleura may occur without discernible cause. It is logical to assume that one important factor favoring spread to the pleura is absence of drainage of the abscess through the bronchial tree. Although our cases are too few for statistical analysis, they suffice to show that extension to the pleura is more common in shut-off abscesses than in abscesses with foul sputum. Pain in the chest was a more frequent and persistent symptom in these than in draining pulmonary abscesses. There were cases in which an unusually virulent infection appeared to exist. In these, severe pain in the chest at the onset and its persistence for days even in the complete absence of cough were evidence of almost immediate spread to the pleura, with the early formation of an empyema.

It was necessary to revert to the question of pain in acute putrid pulmonary abscess, because its correct interpretation has, in our experience, been of value in solving an otherwise difficult diagnostic problem. The differentiation of this pain, when the other features of the case have been considered, from that of the pleuritis which accompanies pneumococcus or other forms of pneumonia has usually been possible. In shut-off acute putrid pulmonary abscess, pain often is apoplecticiform in suddenness and severity and is incapacitating. Once established, it tends to persist for days or weeks. It may remain fairly severe or may vary considerably, but it usually continues.

Physical examination is not of decisive diagnostic assistance. However, in the presence of a pleural infection (empyema) there may be cyanosis, dyspnea and grunting respirations, and the trachea and mediastinal structures may be displaced. Examination of the chest may reveal

little or nothing abnormal, dulness, abnormal breath sounds and rales may be found. When considerable fluid is present in the parietal pleural cavity, the well known signs may be found. A splash may be audible on succussion or indeed may be described by the patient if fluid and air coexist. A symptom of some importance as evidence of a severe pleural infection is localized tenderness of the thoracic wall in the region of severe pain. This, however, occurs in nonputrid pleural infections as well. That clubbing of the digits is likely to occur early in the course of putrid pulmonary infection and at times to be of diagnostic importance is well known. The absence of clubbing has no weight in a decision for or against a putrid infection.

The densities and rarefactions seen on roentgenographic examination in cases of shut-off abscess may be difficult to interpret. They are of no aid in a differentiation between a putrid and a nonputrid infection. When the pulmonary lesion is small, its roentgenographic counterpart is relatively insignificant. In 1 case nothing more than a small area of pulmonary infiltration was observed. In another, in which a large abscess was subsequently demonstrated, an extensive subapical density with the characteristics of a tuberculous or neoplastic infiltration was seen. A fluid level in an abscess cavity usually means a fairly free communication with a bronchus. In most cases of shut-off pulmonary abscess the complicating pleural involvement obscures or modifies the pulmonary shadow to such a degree that it becomes unrecognizable in films. The familiar shadows of a localized or total pleural effusion or hydropneumothorax may be seen. The presence of multiple fluid levels usually means a loculated pyopneumothorax. A roentgenologic picture which often is difficult to interpret is seen in cases of intrapulmonary or interlobar pyopneumothorax. In such instances the general impression is that of a large pulmonary abscess with a fluid level. In all cases of suspected putrid pulmonary infection lateral and oblique views of the thorax and occasionally sectional roentgenograms are necessary for correct interpretation and accurate localization of the lesion.

The preceding discussion of the features of shut-off putrid pulmonary abscess must create the impression that the clinical picture is subject to great variation, and that is quite true. The diagnosis can be predicated only on an awareness that the lesion may exist. It is not too much to say that the features just discussed must be kept in mind in all cases of acute pulmonary infection in adults, conceding the fact that pneumonia or bronchopneumonia due to various organisms is

much more common than shut-off putrid abscess. The occasional occurrence of shut-off pulmonary abscess, the tragedy that often results if the diagnosis is long delayed and the recovery that may be anticipated with reasonably prompt diagnosis and therapy warrant careful consideration of the existence of a lesion. Attention should be all the more focused on the possible existence of a shut-off abscess in cases with some of the features of abscess and with no response to chemotherapy.

The history of persistent pain in the chest, the physical finding of flatness on percussion and the roentgenographic demonstration of pleural fluid point to a complicating pleural infection of a shut-off pulmonary abscess. The extent and character of the empyema are variable. In most cases the empyema is extensive but not total. Air often accompanies the fluid. At operation the external surface of the parietal pleura may reveal acute inflammatory changes and edema. Entrance into the empyema usually is signaled by the escape of very foul thin fluid and air. At other times there may be a large quantity of serous nonodorous sterile fluid in the pleura, or such fluid may be loculated about a smaller collection of foul fluid. In impending perforations of the abscess into the pleural cavity, clear fluid with a faint foul odor may be observed. The sterile fluid is a "sympathetic" effusion. Its presence indicates severe pleural irritation. After evacuation of an empyema the partially collapsed lung covered by necrotic material may be seen. A shallow or moderately deep dirty excavation in the pulmonary parenchyma (the abscess) may be discernible, or a small opening may lead to a large underlying lesion.

The presence of a complicating pleural infection in cases of shut-off abscess suggests that by aspiration of the chest the character of the fluid can be ascertained and the diagnosis of a putrid infection established. The aspirating needle is a valuable but dangerous diagnostic instrument. To use the instrument intelligently one must take great care to locate the fluid accurately. Careful roentgenologic study must precede aspiration. In 4 of the cases characterized by empyema, aspiration provided the means for the detection of the putrid infection. In each of these, several aspirations had to be performed before the foul material was reached. Not infrequently only a "sympathetic" effusion is encountered. This should never leave one satisfied that the basic lesion has been discovered. The presence of such fluid always suggests the possibility (or probability) that an empyema may be found at an adjacent site. The danger of thoracentesis in the presence of a putrid pleural

infection is in infection of the thoracic wall. The occurrence of a putrid phlegmon of the wall may prove fatal. Whenever foul fluid has been disclosed by aspiration, immediate operation is imperative, and the tract of the needle is split open at the same time.

The diagnosis in our cases of shut-off abscess was based on the long interval between the onset of the disease and the appearance of foul sputum or of putrid empyema. In 5 of the 10 cases foul sputum was expectorated between five and sixteen weeks after the onset, and the diagnosis was thereby established. In 4, foul pleural fluid was aspirated. In 1 case, the diagnosis was determined only at autopsy. In another (not included in this compilation), observed in the hospital for many weeks, the abscess was still almost completely confined to the lung when aspiration unexpectedly revealed foul pus.

The treatment of acute putrid pulmonary abscess is often surgical. It is not necessary to present the detailed evidence for the view we hold, for this has been presented elsewhere.<sup>8</sup> The almost uniform satisfactory response to operation and the low operative risk must be balanced against the dangers inherent in a policy of watchful waiting. In any event, operation is imperative for shut-off abscess. In 2 of the 10 cases operations were not performed, in 1 because the expectoration of foul sputum on one occasion after four weeks of mild illness represented the evacuation and spontaneous subsidence of a small abscess and in the other because the diagnosis was not made. In all the others operation was performed as soon as the diagnosis of putrid pulmonary abscess with or without empyema was made.

In this series of 10 cases there were 2 deaths, 1 of which was avoidable.<sup>9</sup> The diagnosis was not made in case 3. The autopsy disclosed a small ruptured putrid abscess and a large putrid empyema. In case 5, which was encountered early in our experience, death occurred several weeks after drainage of a small empyema. In that instance, it was not possible to locate the main focus of disease. A ruptured pulmonary abscess and another putrid empyema were not found until postmortem examination. In this instance present day methods of locating intra-thoracic lesions might have led to drainage of the unopened foci.

There can be anticipated a significant improvement in a patient's condition within a few days

<sup>8</sup> Neuhof, H., and Hurwitt, E. *Ann Surg* **118** 656, 1943.

<sup>9</sup> Four recently observed operative cases, none of them fatal, can be added.

after the operation and a virtual complete subsidence of symptoms and signs referable to the abscess within about two weeks. In the absence of these favorable developments an undrained focus can be assumed to be present. The uniform and rapid clinical improvement of seriously ill patients with putrid pulmonary infections after adequate surgical drainage should provide the necessary stimulus to early diagnosis and treatment.

Shut-off lesions comprise about 5 per cent of all the acute putrid pulmonary abscesses which we have observed in the hospital. The subjoined table offers a summary of 10 well documented cases in our records. A number of additional cases of shut-off abscess were not included because of incomplete data. The following 2 cases have been selected as illustrative of the problems which arise in the diagnosis and the management of shut-off putrid pulmonary abscess.

**CASE 1**—The patient was a 43 year old man whose illness started ten weeks before his admission to the hospital with cough, fever, chilly sensations and stabbing pain in the upper right side of the chest and behind the right shoulder. The pain recurred mildly from time to time. The cough and expectoration became more severe, and numerous small hemoptyses occurred. A foul odor was never observed. Fever and loss of weight finally brought the patient to the hospital.

Examination revealed a chronically ill man, with moderate gingivodental disease. Physical examination showed that the lungs were clear. The patient remained in the hospital for six weeks before a diagnosis was established. He had a low grade fever and continued to sweat and lose weight. The cough varied in severity but was generally rather severe. From 5 to 14 ounces (150 to 420 cc) of nonodorous purulent sputum was expectorated daily. Repeated search for tubercle bacilli revealed no organisms. Occasional mild pain in the chest was experienced. Bronchoscopic examination was performed on four occasions. Purulent material without a foul odor was seen coming from the paravertebral branch of the bronchus of the upper lobe of the right lung. Numerous roentgen examinations revealed only an area of pneumonic infiltration in the posterior portion of the axillary part of the upper lobe of the right lung. The lesion did not change in size. Bronchography with iodized poppyseed oil was not helpful. One day, sixteen weeks after the onset, the patient expectorated several ounces of extremely foul sputum. Roentgenograms now revealed a large cavity, with a fluid level at the site of the previously observed infiltration.

Thoracotomy and pneumonotomy, performed after mobilizing the scapula, revealed a pulmonary cavity containing inspissated foul pus. The lining of the abscess was partly sloughing and partly smooth and glistening. Numerous bronchial openings were visible. After being completely unroofed, the cavity was packed.

The postoperative course was prolonged, and the abscess cavity closed slowly. At follow-up examination fifteen months later, the operative incision was found to be healed and the patient was asymptomatic.

This case is unique and is the only one in our series that demonstrates the development under

observation of a subacute or almost chronic putrid pulmonary abscess without foul sputum. The failure of this abscess to extend to the pleura to form an empyema also is exceptional. The fact that the diagnosis could not be established despite four bronchoscopic examinations is evidence of a completely shut-off putrid pulmonary abscess.

her readmission, the pain suddenly became extremely severe and the temperature rose to 105 F.

On her admission the patient was cyanotic and tachypneic. The mediastinal structures were shifted to the right, and there were signs of pleural fluid over the entire left side of the chest. The thoracic wall was tender. Clubbing of the digits was not present. Roentgen examination revealed a diffuse clouding of the entire left side of the chest.

*Putrid Pulmonary Abscess Without Foul Sputum: An Outline of Ten Cases*

Case	Onset	Pain	Cough	Expectoration	Hospital Stay Before Diagnosis, Days	Duration of Disease	Roentgenographic Appearance	Size of Pulmonary Abscess	Extent of Pleural Infection	Result
1	Cough, gradual	At onset for a few days, mild	Persistent and moderately severe	Profuse but nonfoul except just preceding operation	42	16 weeks	Pneumonic infiltration	Large	None	Recovery
2	Pain, sudden	Moderate for 20 weeks at onset	Persisted mildly after second week	1 to 3 oz (3 7 to 11 1 cc) daily, nonfoul except once 6 weeks after onset	14	6 weeks	Small pneumonic infiltration	Small	None	Recovery
3	Pain, sudden	Severe at onset, persisted mildly	Mild, beginning 3 days after onset	Not foul, 1 to 3 oz daily	17	20 days		Small	Moderate parietal empyema	Death, patient not operated on
4	Infection of upper respiratory tract, gradual	1 week after onset, severe, persisted with remissions and exacerbations	Mild from onset, persistent	Scant, nonfoul	Diagnosis on admission	5 weeks	Pneumonic infiltration and pleural effusion	Small	Total, parietal empyema	Recovery
5	Infection of upper respiratory tract and pain, gradual	Gradually increasing severity, persistent	Mild	Scant, nonfoul	10	24 days	Pleural effusion, later fluid levels appeared	Moderate	Moderate, interlobar and infrapulmonary empyema	Death, undrained pulmonary abscess and empyema
6	Cough, gradual	Severe, 2 weeks after onset, persistent with exacerbations and remissions	Mild for 2 weeks and then stopped	Scant, questionably foul on 1 occasion 2 weeks after onset	Diagnosis on admission	4 weeks	Pneumonic infiltration and small pleural effusion	Moderate	Moderate parietal empyema	Recovery
7	Cough, gradual	Severe for 2 weeks after onset	Moderate from onset	Several ounces daily, foul immediately before operation	1	15 days	Pleural effusion	Large	Moderate parietal empyema	Recovery
8	Cough and fever, gradual	Began 2 weeks after onset, mild for 3 weeks, then severe	Mild but persistent	Scant, not foul	11	8 weeks	Loculated pyopneumothorax	Small	Moderate, infrapulmonary empyema	Recovery
9	Cough and fever, gradual	Started 2 weeks after onset, severe, recurred from time to time for 6 weeks	Mild but persistent	Scant, not foul until 8 weeks after onset	42	8 weeks	Effusion, later loculated pyopneumothorax	Moderate	Moderate interlobar empyema	Recovery
10	Pain, sudden	Severe, remissions for 5 weeks	Slight, 4½ weeks after onset	Scant, not foul	Diagnosis on admission	5 days	At first pneumonic infiltration, later fluid level	Very large	None	Recovery

CASE 2—Six weeks before her admission to the hospital, this 60 year old woman had a thyroidectomy under general anesthesia. The postoperative course was complicated by a ten day febrile episode characterized by slight cough without expectoration and by indefinite mild discomfort in the left side of the chest. Roentgen examination revealed an area of pneumonic infiltration in the lower lobe of the left lung. The temperature gradually subsided, and the patient was discharged from the hospital. Thereafter she experienced intermittent mild discomfort in the left part of the chest, occasional cough and low grade fever. Two days before

The patient was observed for the next two weeks, during which time she remained acutely ill. The pain diminished in severity but persisted, and the cough increased somewhat, but nothing more than scant non-odorous sputum was expectorated. Subsequent roentgenograms revealed the development of a large fluid level. The temperature varied between 102.5 and 100 F. Five thoracic taps were done, but only turbid nonfoul sterile pleural fluid was obtained. Sulfapyridine did not affect the clinical course. Finally, the sixth tap, two weeks after admission, disclosed foul pus, and immediate operation was performed.

A parietal 'sympathetic' effusion was traversed before a large infrapulmonary pyopneumothorax was entered and drained. A small, perforated putrid pulmonary abscess was seen on the inferior surface of the lower lobe, and this was unroofed. All the recesses of the pulmonary cavity and the infected pleura were packed.

The drained areas soon became clean. A bronchial fistula was present for several days. There was rapid symptomatic improvement. The patient was discharged in three weeks. Follow-up examination six weeks later revealed the patient to be in excellent condition and the wound completely healed. The patient was found to be well at a follow-up examination one year after her operation.

The history, the clinical and roentgenographic data, the operative findings and the postoperative course are characteristic of shut-off acute putrid pulmonary abscess with putrid empyema. The site of perforation in the infrapulmonary space led to a localized collection of pus situated away from the parietes. It was for this reason that only "sympathetic" fluid was so often withdrawn on exploratory puncture.

#### SUMMARY

The early appearance of fetid sputum establishes the diagnosis of acute putrid pulmonary abscess in the great preponderance of cases. Foul sputum does not appear at all or makes its

appearance much later than usual in about 5 per cent of the cases. On the basis of the assumed mechanism, the term shut-off pulmonary abscess appears appropriate for such cases. The great tendency of shut-off abscesses to invade the pleura comprises a special feature. The clinical manifestations with and without pleural invasion and the difficulties in diagnosis in the absence of fetid sputum must be carefully considered. The diagnosis should be entertained when (1) a cause for a putrid pulmonary abscess exists (or, in the absence of a cause, dental hygiene is poor), (2) thoracic pain is severe, prolonged or recurrent, (3) cough and expectoration are minimal or absent, and (4) the roentgenogram reveals persistent pulmonary infiltration with or without pleural effusion. There are grave dangers inherent in a too long delayed diagnosis, but there is a likelihood of a correct diagnosis if the possibility of this lesion is borne in mind. The excellent results which can be achieved by adequate operations on the pulmonary abscess as well as on the complicating empyema, which is often present, provide an additional incentive to establishing the diagnosis of shut-off putrid pulmonary abscess.

# SULFONAMIDE COMPOUNDS AND PENICILLIN

## THE EFFECT OF COMBINED THERAPY ON EXPERIMENTAL INFECTIONS IN MICE

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Penicillin and one of the sulfonamide compounds are frequently used simultaneously in treatment of serious infections in an attempt to enhance the therapeutic effect. Ungar,<sup>1</sup> in 1943, reported that sulfapyridine potentiated the action of penicillin, both in vitro and in a limited number of infected mice. Soo-Hoo and Schmitzer<sup>2</sup> confirmed Ungar's claim that penicillin and various sulfonamide drugs were synergistic in combatting streptococcal infections in mice. They also showed that penicillin could prevent the inhibiting action of paraaminobenzoic acid on the sulfonamide drugs. This observation suggested that, although penicillin and the sulfonamide drugs are presumed to act by different mechanisms, the combined effect might be greater than a summation and might represent a potentiation due to the inhibition by penicillin of the action of paraaminobenzoic acid present in pus and exudates and even in normal tissue fluids. T'ung<sup>3</sup> studied the in vitro effects of sodium sulfathiazole and of penicillin alone and in combination, on several strains of *Brucella* organisms. In about half the strains there was susceptibility to the drugs individually, and there was an enhanced bactericidal effect when the combination was used. In similar in vitro studies on *Actinomyces bovis* and related organisms, Dobson and Cutting<sup>4</sup> were unable to demonstrate any important increase in inhibi-

tion when sulfonamide compounds and penicillin were used simultaneously.

Because of the therapeutic implications in the suggestion of additive or synergistic effects through the use of the two chemotherapeutic agents together, the problem was studied in bacterial infections in mice.

### REPORT OF EXPERIMENTS

**Pneumococcal Infection**—White mice weighing about 20 Gm each were given intraperitoneal injections of 0.5 cc of a 1:100 dilution of a twenty-four hour culture in blood broth of pneumococcus type I recently isolated from a patient. One or two days later, depending on when the mice showed signs of severe illness, treatment was started. In series 200 and 201, 10 mg of sodium sulfadiazine or 10 units of penicillin, or both, was injected subcutaneously twice daily for four days. In series 202, 203, 205 and 206, 5 mg of sodium sulfadiazine or 20 units of penicillin, or both, was injected subcutaneously twice daily for four days. In each series, the control group and each test group consisted of 5 or 10 mice. The results, based on the number of mice surviving after one week, showed a slightly enhanced effect with the combined drugs (table 1). Larger doses of penicillin (50 to 100 units twice daily) saved all mice.

TABLE 1—Survival of Mice After Pneumococcal Infection when Treated with Sodium Sulfadiazine or Penicillin or with Both

Series	No of Animals in Each Group	Number of Animals Surviving 7 Days			
		Control	Sodium Sulfadiazine, Mg Twice Daily	Penicillin, Units Twice Daily	Sodium Sulfadiazine Plus Penicillin
200	5	1	5 (10)	2 (10)	3
201	5	0	2 (10)	0 (10)	2
202	5	0	0 (5)	0 (20)	2
203	5	1	2 (5)	0 (20)	3
205	5	0	1 (5)	1 (20)	2
206	10	0	4 (5)	2 (20)	5
Percentage surviving		6	40	14	50

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1 Ungar, J. Synergistic Effect of Para-Aminobenzoic Acid and Sulfapyridine on Penicillin, *Nature*, London **152** 245 (Aug 28) 1943

2 Soo-Hoo, G, and Schmitzer, R J. The Activity of Penicillin Combined with Other Anti-Streptococcal Agents Towards  $\beta$ -Hemolytic Streptococci in Vivo, *Arch Biochem* **5** 99 (Sept) 1944

3 T'ung, T. In Vitro Action of Penicillin Alone and in Combination with Sulfathiazole, on *Brucella* Organisms, *Proc Soc Exper Biol & Med* **56** 8 (May) 1944

4 Dobson, L G, and Cutting, W C. Penicillin and Sulfonamides in the Therapy of Actinomycoses. Report of Sixteen Additional Cases and in Vitro Tests of the Susceptibility of *Actinomyces* to Penicillin and Sulfadiazine, to be published

**Streptococcal Infection**—White mice weighing about 20 Gm each were given intraperitoneal injections of 0.5 cc of a 1:100 dilution of a twenty-four hour culture of G 27 K hemolytic streptococci. About six hours later treatment was started. In series 210, a dose of 5 mg of sodium sulfadiazine or 20 units of penicillin, or both, was injected subcutaneously, twice daily for two or three days. In series 211, 212, 213 and 214, the dose of sodium sulfadiazine was 0.5 mg and the

penicillin was increased to 30, 40, 50 and 60 units twice daily respectively. In each series, the control group and each test group consisted of 5 or 10 mice. The results, based on the number of mice surviving after one week, showed that the combination of penicillin and sodium sulfadiazine was slightly superior to the individual drug (table 2). In the higher doses penicillin alone saved all the animals.

TABLE 2—*Survival of Mice After Streptococcal Infection when Treated with Sodium Sulfadiazine or Penicillin or with Both*

Series	No. of Animals in Each Group	Number of Animals Surviving 7 Days			
		Control	Sodium Sulfadiazine, Mg Twice Daily	Penicillin, Units Twice Daily	Sodium Sulfadiazine Plus Penicillin
210	5	1	4 (5)	0 (20)	1
211	5	0	2 (0.5)	0 (30)	3
212	5	0	1 (0.5)	0 (40)	2
213	10	1	8 (0.5)	7 (50)	10
214	5	1	2 (0.5)	2 (60)	4
Percentage surviving 10			56.6	30	76.6

#### COMMENT

The frequent clinical policy of using sulfonamide drugs and penicillin simultaneously is given a measure of support by the experimental results obtained. With both pneumococcal and streptococcal infections in mice, combined therapy in the doses used resulted in slightly better percentages of survival than therapy with either drug alone. While larger doses of either single drug might have given equally good or even better results, the experimental results still have clinical significance.

The doses of sodium sulfadiazine used, 1 to 10 mg. daily for a 20 Gm mouse, are proportional on a weight basis to a daily dose of 3.5 to 35 Gm for a 70 Kg man. Although sulfonamide drugs are better tolerated by small animals than by human beings, the higher doses approach the margin of safety, and the combinations would obviously be superior to an increased

dose of the sulfonamide drug. The doses of penicillin, 20 to 200 units daily, are similarly proportional to 70,000 to 700,000 units daily for an adult man. With the larger doses, all the animals were saved, and therefore no enhancement of action by the combination could be demonstrated. Nevertheless, even though these large doses are nontoxic, for infections with organisms more resistant to penicillin, for mixed bacterial infections or for grave illnesses, the most effective action of penicillin may not be obtained with them and combined therapy may be valuable. However, for highly susceptible infections, the combination would appear to offer no advantages and to possess the disadvantage of possible toxic effect from the sulfonamide drug.

The total effect of the combination of penicillin and a sulfonamide drug is far short of the sum of the individual effects, and potentiation, therefore, in the sense of an effect greater than an additive effect, is absent.

#### CONCLUSIONS

Pneumococcal and streptococcal infections in mice responded slightly more favorably to simultaneous treatment with penicillin and sulfadiazine than to treatment with either drug alone.

When doses comparable to those tried are used clinically, some enhancement of therapy may be expected from the combination.

Even when higher doses of penicillin are used, the desperate state of the patient or the resistance of the particular causative organism or organisms may warrant combined therapy.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

# TULAREMIC MENINGITIS

## REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS

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Tularemia has been accepted generally as a systemic disease which frequently presents manifestations that may be interpreted as being septicemic in nature. It is logical, therefore, to suspect in case of a septicemic disease such as tularemia that almost every tissue of the body at some stage of the illness may be infected. Although evidence of meningeal irritation and involvement of the central nervous system are occasionally observed in cases of tularemia which terminate fatally, instances in which the existence of tularemic meningitis has been proved, either during life or by postmortem studies, are unusually rare, especially when one considers the frequency with which the lungs, liver, spleen and lymph nodes are involved in fatal cases of tularemia. Because invasion of the meninges by *Bacterium tularensis* (*Pasteurella tularensis*) has been observed so infrequently, we have considered it worth while to report this case, which came to our attention in a recent review<sup>1</sup> of the cases of tularemia that have occurred at Charity Hospital since 1928.

As early as 1927, Francis and Callender<sup>2</sup> mentioned a case which was probably an example of tularemic meningitis. Again, in 1930, Francis<sup>3</sup> made mention of 5 fatal cases of tularemia terminating with severe meningeal symptoms. Hazlip and O'Neil<sup>4</sup> in 1931, however, were the first to demonstrate that the meningeal symptoms associated with tularemia

were the result of invasion of the spinal canal by *Bact. tularensis*. Subsequent cases have been reported by Bryant and Hirsch,<sup>5</sup> Hartman,<sup>6</sup> Pund and Hatcher<sup>7</sup> and David and Owens.<sup>8</sup> The last mentioned successfully isolated the infecting organism from the blood and spinal fluid of their 5 year old patient before death occurred. The table summarizes those cases considered acceptable as instances of tularemic meningitis.

### REPORT OF CASE

S. J., a 34 year old Negro man, was admitted to the service for contagious diseases at Charity Hospital on Feb. 16, 1940. The patient had been perfectly well until five days prior to his admission, at which time he had a severe, shaking chill with profuse sweating. Several hours later, he began to have a severe headache, and his wife believed that he had a high fever at that time. The following day he felt well enough to return to work but continued to have a mild headache. No nausea, vomiting, diarrhea, cough, hemoptysis or other symptoms were present. He continued to feel "dumpy" until about thirteen hours before his admission to the hospital, at which time he rapidly became confused and disoriented and failed to recognize familiar people and objects. He apparently failed to hear what was said to him or at least failed to comprehend what was said. He would place his hands over his eyes occasionally and mumble incoherently. He was seen by a physician, who advised him to come into the hospital for treatment. The patient's past history and family history were noncontributory.

On admission to the hospital, he was observed to be a well developed, well nourished Negro man, 34 years of age, who was uncooperative, agitated, confused and disoriented and had to be restrained. His temperature was 100.4 F by mouth, pulse rate 58 per minute and respiratory rate 20. The blood pressure was 130 systolic and 82 diastolic. The pupils reacted to light. There was no rigidity of the neck and no lymphadenopathy. Auscul-

5 Bryant, A. R., and Hirsch, E. F. Tularemic Leptomeningitis. Report of Case, *Arch. Path.* **12**: 917 (Dec.) 1931.

6 Hartman, F. W. Tularemic Encephalitis. Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, *Am. J. Path.* **8**: 57 (Jan.) 1932.

7 Pund, E. R., and Hatcher, M. B. Tularemic Meningitis. Report of Case with Postmortem Observations, *Ann. Int. Med.* **10**: 1390 (March) 1937.

8 David, J. K., and Owens, J. N. Tularemic Meningitis. Report of a Case and Summary of Previously Reported Cases, *Am. J. Dis. Child.* **67**: 44 (Jan.) 1944.

From the Department of Medicine, Tulane University or Louisiana School of Medicine and Charity Hospital.

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4 Hazlip, J. O., and O'Neil, A. E. A Case of Meningitis Due to *Bacterium Tularensis*, *J. A. M. A.* **97**: 704 (Sept. 5) 1931.

tation and percussion revealed clear pulmonary fields. The heart rhythm was regular. There were no murmurs. Examination of the abdomen revealed no tender areas, masses or distention. The extremities were normal. The deep tendon reflexes were sluggish, and Kernig's and Brudzinski's signs were absent.

Laboratory studies at the time of the patient's admission revealed a hemoglobin content of 14.4 Gm per hundred cubic centimeters and a white cell count of 11,200, with 81 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes and 3 per cent monocytes. Examination of the urine revealed no abnormalities. The serologic reaction of the blood was negative for syphilis by both the Kline and the Kolmer test. Lumbar puncture on the day of his admission yielded spinal fluid under a pressure of 34 cm of water, of turbid appearance and containing 960 white cells, with 60 per cent large lymphocytes and 40 per cent small lymphocytes. There was a 4 plus reaction for globulin. The value for sugar was 45.4 mg per hundred cubic centimeters and for chlorides 643 mg per hundred cubic centimeters, and the colloidal gold curve was 00012340220. A smear of the spinal fluid showed no organisms. Culture of the fluid showed no growth in twenty hours.

Several hours after his admission, the patient was still restless and agitated and was given paraldehyde. Lumbar puncture was repeated on February 17, with results similar to those of the previous day. On February 18 the patient began spitting up frothy, bright red blood. The respiration and pulse were poor, some degree of rigidity of the neck was noted, and examination of the chest still revealed nothing abnormal. The patient became comatose, and fluids were administered intravenously. On February 19 he had two generalized convulsions in thirty minutes. Breathing was stertorous. Seven and one-half grains (0.5 Gm) of sodium amytal was given. An infusion of 3,000 cc of 10 per cent dextrose in isotonic solution of sodium chloride was given. The white blood cell count was 14,100. On February 20 the patient's condition became much worse. Administration of oxygen by nasal catheter was begun on February 21. The white blood cell count was 9,400. The urine was normal. A spinal tap revealed that the cerebrospinal fluid was still turbid, 400 cells were present, and pressure was 24 cm of water. Rales were heard bilaterally. A roentgenogram of the chest was interpreted by the roentgenologist as "showing increased density in the left lung from the level of the third to the level of the sixth rib anteriorly and slightly increased density of the right side in the perihilar zone. The picture was not characteristic of tuberculosis and was suggestive of pneumonia of the left lung." Full doses of sulfapyridine were prescribed and were given by the intravenous route. Infusions were continued. On February 22, the eleventh day of illness, the patient died.

Postmortem examination was performed by Dr. Emil Palik, of the department of pathology of the Charity Hospital, approximately five hours after death occurred. Following is the autopsy protocol.

**Gross Pathologic Changes**—Body. The body was that of a well developed, well nourished Negro man, 34 years of age, measuring 175 cm in length and weighing 152 pounds (69 Kg). Rigor mortis was present and also body heat. The pupils were round and equal and measured 3 mm each. The scleras were clear. The abdomen was flat. No edema was present. Oral hygiene was poor. The extremities and external genitalia revealed nothing unusual.

**Peritoneal Cavity**. The membranes of the peritoneal cavity were smooth and glistening. There were no adhesions or free fluid. The appendix, omentum and

mesenteric lymph nodes appeared normal. The diaphragm extended to the fifth rib on the right and the sixth interspace on the left.

**Pleural Cavities**. The membranes of the pleural cavities were smooth and glistening. No free fluid or adhesions were present, and the lungs completely filled the cavities.

**Pericardial Cavity**. The pericardial surfaces were smooth and glistening. The pericardial sac was normal in size, shape and position. There was no free fluid or adhesions.

**Heart**. The heart weighed 350 Gm. The valves, endocardium and coronary arteries presented no significant abnormalities. The myocardium was pale red and firm.

**Aorta**. The aorta presented numerous small, pale yellow, atheromatous plaques.

**Lungs**. The right lung weighed 1,100 Gm, the left weighed 850 Gm. The surfaces were smooth and dark red. On section, all lobes in both lungs presented confluent large and small dark red areas of consolidation. Some of these areas appeared moist, others, dry and granular. The hilar lymph nodes were edematous. The bronchial tree contained mucoid exudate. The vessels appeared normal.

**Spleen**. The spleen weighed 190 Gm, it was dark red and moderately firm. On section, the malpighian corpuscles appeared prominent. No abnormalities were seen throughout the pulp, and the pulp scraped with moderate difficulty.

**Liver**. The liver weighed 2,100 Gm. It was reddish brown and moderately firm. On section, the normal architecture was seen. The gallbladder appeared normal and contained dark brown bile. The biliary tract and portal vein were normal.

**Pancreas**. The pancreas weighed 70 Gm, it was moderately firm and pale gray. On section, the normal architecture was seen.

**Gastrointestinal Tract**. The gastrointestinal tract was normal in its entirety.

**Adrenal Glands**. The adrenal glands weighed 10 Gm each. They were tan colored and soft. On section, the normal line of demarcation between cortex and medulla was seen.

**Kidneys**. The right kidney weighed 190 Gm, the left weighed 210 Gm. They were pale red and moderately firm. The capsules stripped with moderate difficulty, revealing finely granular renal surfaces. On section, the cortices were found to measure 8 mm each and were clearly demarcated from the medullas. The cortical striations were normal. The calices, pelvis and ureters appeared normal.

**Urinary Bladder**. The urinary bladder contained a small amount of clear straw-colored urine. The mucosa was pale gray and smooth. The ureteral and urethral orifices were patent.

**Genital Organs**. The prostate, testes, seminal vesicles and urethra were normal.

**Brain**. When the calvarium was removed, the meninges were found to be intact, and when they were opened the cerebrospinal fluid was found to be clear. The brain itself weighed 1,470 Gm. The subarachnoid vessels were greatly dilated. The hemispheres were symmetrically developed. Over both of these there were a few patches of grayish white exudate, especially over the frontal region. These were limited to the sulci. There was no exudate apparent grossly at the base of the brain. No softenings could be felt. On section, no abnormalities could be seen within the brain substance and ventricles.

# Summary of Reported Cases of Tularemia Meningitis

Author	Sex	Race	Age	Source of Infection	Form of Disease	Duration of Disease Before Meningitis Developed, Days	Duration of Meningitis Before Death, Days	Spinal Fluid	Blood Counts	Agglutinations and Cultures of the Blood	Diagnosis Established
Hatzlip and O'Neill <sup>4</sup>	M	W	45	Rabbits and squirrel	U G	5	5	Cloudy, 2,100 cells, 70% polymorphonuclears, stain and culture negative	3,300 white blood cells, 60% polymorphonuclears, lymphocytes 36%, monocytes 2%	Agglutination in dilution of 1:40, culture of blood negative	Spinal fluid injected into guinea pig with positive reaction for tularemia
Bryant and Hirsch <sup>5</sup>	M	W	18	Rabbit	U G	10	5	Cloudy, 400 cells, 84% monocytes, 10% polymorphonuclears, smear and culture negative, 230 mm water pressure, Pandey reaction positive, 75 mg per 100 cc albumin		Agglutination in dilution of 1:40 on 11th day	Inoculation of guinea pigs (postmortem) from splenic tissue of patient reproduced disease, focal lesions in meninges
Hartman <sup>6</sup>	M	W	Middle aged	Middle Rabbits	U G	1	25	Bloody fluid, 145 white blood cells, culture of fluid negative, sugar 12 mg per 100 cc	11,500 white blood cells, 84% polymorphonuclears, lymphocytes 2%, monocytes 14%	Agglutination in dilution of 1:640 on 15th day, 1:1,280 on 17th day, culture of blood negative	Rising agglutination titers, lesions at necropsy interpreted as tularemia
Pand and Hatcher <sup>7</sup>	F	N	12	?	U G	7	3	114 cells, 18 mm mercury pressure, negative for globulin Wassermann reaction negative, 200 cells, 22 mm mercury pressure, smear negative	8,700 white blood cells, 65% polymorphonuclears, lymphocytes 35%	Culture of blood negative	Necropsy showed appendix, thymus, brain and uterus involved, blood agglutination in dilution of 1:640 and 1:1,280
David and Owens <sup>8</sup>	F	W	5	Cat that had fed on rabbit viscera	U G	9?	4	Cloudy, 2,000 cells, 99% lymphocytes, 18 mg per 100 cc sugar, 4+ Pandey reaction, culture positive for Bac. tularensis	17,000 white blood cells, 80% polymorphonuclears, lymphocytes 15%, monocytes 5%	Culture of blood positive on 2d day, culture positive on 4th day, sputum positive, culture of pus from the thumb positive	Culture of blood, sputum, pus from the thumb and spinal fluid positive, postmortem examination confirmatory
Stuart and Pullen	M	N	34	?	T	5	6	Cloudy 960 cells, 60% large lymphocytes, 40% small lymphocytes, 4+ globulin reaction, 45 mg per 100 cc sugar, 643 mg per 100 cc chlorides, smear and culture negative, colloidal gold curve, 00012340220	11,200 white blood cells, 81% polymorphonuclears, lymphocytes 16%, monocytes 3%	Culture of blood negative, no agglutination	Postmortem inoculation of laboratory animals

\* U G indicates ulceroglandular, T indicates typhoidal

*Microscopic Examinations*—Heart The myofibrils, connective tissue and vessels appeared normal

Lungs In some areas the alveoli and bronchioles appeared normal In other areas, the alveoli were filled with polymorphonuclear leukocytes and a small amount of fibrin In some areas, the alveolar septums had been destroyed Numerous macrophages containing tiny brown granules of pigment were present The bronchioles contained acute inflammatory exudate and debris The vessels appeared normal

Spleen The capsule, trabeculae, malpighian corpuscles and vessels appeared normal No foci of necrosis were present

Liver The hepatic cords, portal spaces, central veins and sinusoids appeared normal The submucosa and muscularis of the gallbladder were infiltrated by a moderate number of lymphocytes and plasma cells

Miscellaneous Observations The cells of the cortex and medulla of the adrenal glands appeared normal, as did the mucosa and muscularis of the intestine

The islets, acini, connective tissue and vessels in the pancreas, the glomeruli, tubules and arterioles of the kidneys, the prostate lobules and stroma and the epididymal lobules and stroma all appeared normal

Brain In the meninges of most sections of the brain there were a few small and large round mononuclear cells, inflammatory in character There was an abundance of yellow pigmented granules, some of which were free and some inside the large mononuclear cells This infiltration was most severe in the choroid plexus Here also were seen numerous psammoma bodies All sections of the cortex showed extreme congestion and severe degeneration of ganglion cells, the latter being greatly out of proportion to the degree of inflammation This swelling and disappearance of ganglion cells was also noted in the basal ganglions and in the brain stem The ependyma of the lateral ventricles showed plaque formation and subependymal gliosis In the medulla there were several subependymal petechiae

*Postmortem Bacteriologic Observations*—Culture of the blood showed no growth Culture of the lungs revealed streptococci Guinea pigs inoculated with substance from the lungs and the brain became ill and were examined by autopsy on the fourth day Each showed numerous miliary lesions in the spleen consistent with the diagnosis of tularemia

#### COMMENT

There was no clue as to the mode of infection in this case, and, since no evidence of ulceration or regional lymphadenopathy was present, tularemia was not considered as a diagnostic possibility Although an occasional report<sup>9</sup> of meningeal symptoms associated with the typhoidal type of tularemia has appeared, this is, to our knowledge, the first proved instance of tularemic

meningitis in which ulceration or regional lymphadenopathy was lacking

One can determine from the table that the average duration of illness in 6 cases of tularemia before evidences of meningeal involvement appeared was seven days Whether this may be interpreted as additional evidence in favor of a second bacteremia or invasion of the blood stream by *Bact tularensis* five or six days before death in fatal cases, as postulated by Foshay,<sup>10</sup> we are unable to state

In an attempt to explain the pathogenesis of the meningeal involvement in cases of tularemia three possible routes of invasion have been suggested David and Owens<sup>8</sup> have expressed the opinion that the infecting organism may have been introduced into the subarachnoid space at the time of the initial lumbar puncture in their case, since bacteremia was present when the patient entered the hospital Pund and Hatcher,<sup>7</sup> in interpreting their case, considered the meningitis secondary to the breakdown of an area of focal necrosis in the substance of the brain The other suggested explanation is that the infecting organism reached the meninges directly by way of the blood stream<sup>8</sup> In a disease in which evidences of bacteremia occur with considerable frequency, involvement of the meninges is to be expected in a certain number of cases Tularemia is to be considered, therefore, in the diagnosis of obscure forms of meningitis, and, in turn, evidences of meningeal involvement should be sought for in gravely ill patients with tularemia

Thus far, no patients with tularemic meningitis have recovered Therapy is of no avail, though one should utilize all available chemotherapeutic agents, including penicillin and the sulfonamide compounds, and Foshay's antiserum

#### SUMMARY

A case of tularemic meningitis was observed and studied Five previous cases were collected from the literature To our knowledge, our case is the first in which tularemic meningitis occurred in the typhoidal form of the disease

9 Tillisch, J H Case of Typhoid Tularemia, Proc Staff Meet, Mayo Clin 16 205 (March 26) 1941

10 Foshay, L Tularemia A Study of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in 600 Patients, Medicine 19 1 (Feb) 1940

# INTRAVENOUS INJECTION OF ACACIA

## CLINICAL AND PHYSIOLOGIC EFFECTS ON PATIENTS WITH NEPHROTIC EDEMA

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The management of edema in patients with chronic glomerulonephritis complicated by the syndrome of hypoproteinemia and massive proteinuria continues to be unsatisfactory. The immediate cause of the edema is the reduced osmotic pressure resulting from the hypoproteinemia. No clinical methods are available at present by which one can stop the proteinuria or stimulate production of plasma protein so that the plasma protein concentration will rise sufficiently to eliminate the edema.

Administration of acacia in the treatment of nephrotic edema was first reported by Haitmann in 1933<sup>1</sup>. Since that time, many clinical reports have appeared, and much experimental work has been done on this subject. For the most part these reports have been unfavorable, with the result that acacia is not used extensively in the treatment of nephrotic edema. The opposition to the use of acacia is based on the following observations:

1 Cases have been reported in which there was no significant reduction of edema in spite of large doses of acacia.<sup>2</sup>

2 When acacia is administered, there is almost invariably further reduction in the plasma protein concentration.<sup>3</sup>

3 In some patients tenderness and enlargement of the liver follow repeated injections of large doses of acacia.<sup>2</sup>

From the Departments of Medicine and Biochemistry, Howard University School of Medicine and Freedmen's Hospital

1 Hartmann, A F, Senn, M J E, Nelson, M V, and Perley, A M. The Use of Acacia in the Treatment of Edema, *J A M A* **100** 251 (Jan 28) 1933

2 (a) Dick, M W, Warweg, E, and Andersch, M. Acacia in the Treatment of Nephrosis, *J A M A* **105** 654 (Aug 31) 1935. (b) Faulkenstein, D F, and Jackson, R L. Acacia Therapy in a Child with Nephrosis, *J Pediat* **16** 700, 1940

3 (a) Yuile, C L, and Knutti, R E. Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia, *J Exper Med* **70** 605, 1939. Goudsmit, A, Jr, Binger, M W, and Power, M H. Acacia in the Treatment of the Nephrotic Syndrome, *Arch Int Med* **68** 701 (Oct) 1941. Dick, Warweg and Andersch<sup>2a</sup> Faulkenstein and Jackson<sup>2b</sup>

4 In postmortem studies of patients<sup>4</sup> and in experimental studies on dogs,<sup>5</sup> large deposits of acacia have been recovered in the livers. This and the two preceding observations have led to the opinion that acacia causes serious hepatic damage and therefore should not be used in the treatment of nephrotic edema.

In spite of these observations, the use of acacia in the treatment of nephrotic edema has recently been revived by Goudsmit and Binger.<sup>6</sup> Their reports seemed sufficiently encouraging to justify further clinical study.

The data to be reported here indicate that acacia, when combined with mercurophylline injection, is an effective means of treating nephrotic edema, even when other recognized methods of treatment have failed. Further, some of the objections to acacia therapy are shown to be unjustified.

## MATERIALS AND METHODS

The acacia<sup>7</sup> used in this study was dissolved in distilled water and injected intravenously by the Murphy drip method at a concentration of 15 to 20 per cent. Determinations of plasma volume were made by using congo red according to the method of Keith, Rowntree and Geraghty as modified by Harris.<sup>8</sup> Hematocrit studies were done by the method of Wintrobe.<sup>9</sup> The amounts of acacia in plasma and in urine were determined by the method of Butt, Power and Keys.<sup>10</sup> The acacia content of tissues was determined by the same method after extraction of the triturated tissues with hot distilled water. The prothrombin time was measured by

4 (a) Andersch, M, and Gibson, R B. Studies on the Effect of Intravenous Injections of Colloids, *J Pharmacol & Exper Therap* **52** 390, 1934. (b) Dick, Warweg and Andersch<sup>2a</sup> Faulkenstein and Jackson<sup>2b</sup>

5 Yuile and Knutti<sup>3a</sup> Andersch and Gibson<sup>4a</sup>

6 Goudsmit, A, Jr, and Binger, M W. Treatment of Nephrotic Edema, *J A M A* **114** 2515 (June 29) 1940

7 The acacia used in these experiments was supplied by Eli Lilly and Company

8 Osgood, E E. Congo Red Test, in *A Textbook of Laboratory Diagnosis*, ed 3, Philadelphia, The Blakiston Company, 1940, p 413

9 Wintrobe, M M. *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942

10 Butt, H R, Power, M H, and Keys, A. Concentration of Acacia in the Serum, Its Rate of Excretion and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, *J Lab & Clin Med* **24** 690, 1939

the Quick method<sup>11</sup> The total plasma protein was determined by the Kjeldahl method and by direct nesslerization The plasma albumin was determined by the same method after treatment with 22.5 per cent sodium sulfate to remove the plasma globulins The mercurphylline injection<sup>12</sup> was given in distilled water intravenously

OBSERVATIONS

Nine patients with chronic glomerulonephritis, hypoproteinemia and proteinuria and 1 patient with hyperproteinemia were given acacia intra-

TABLE 1—Effect of Intravenous Injections of Acacia on Plasma Protein Concentration

Case	Hours After Injection	Plasma Protein, Gm per 100 Cc	Plasma Acacia, Gm per 100 Cc	Acacia Injected, Gm
1	0	4.68	0.0	60
	20	2.81	2.07	
2	0	2.61	0.0	120
	24	1.98	1.70	
	72	1.96	1.43	
	144	2.93	1.07	
3	0	4.34	0.0	90
	20	2.83	1.37	
	44	2.73	1.41	
4	0	5.0	0.0	90
	24	2.51	1.87	
	72	2.60	1.91	
5	0	3.77	0.3	60
	24	2.35	1.87	
6	0	4.80	0.10	60
	24	3.25	2.02	
7A	0	8.3	0.0	90
	12	7.0	1.37	
7B	0	6.90	1.20	90
	8	5.02	2.61	
	144	6.60		
8	0	4.5	0.0	120
	22	2.5	1.57	

venously on several occasions Observations were made in order to study the effect of injection of acacia on plasma protein concentration, changes in plasma volume, excretion of acacia, edema and proteinuria

Table 1 summarizes the effect of the acacia on the plasma protein concentration in 8 of the patients In all patients studied an immediate reduction in the plasma protein concentration was observed This reduction was demonstrable at any period between eight and twenty-four hours after the injection of acacia After about seventy-two hours the plasma protein concentration showed a slow but progressive rise toward the initial level

This type of reduction in plasma protein concentration has been previously reported and is cited as one of the major contraindications of acacia therapy for patients whose concentration is already below the critical level Some authors

11 Kracke, R. R., and Parker, E. P. Textbook of Clinical Pathology, ed. 2, Baltimore, Williams & Wilkins Company, 1940, p. 142

12 The preparation used was Mercupurin, supplied by Campbell Products, Inc.

have interpreted this as evidence of hepatic damage Certain of our data indicate that most of this depression in plasma protein can be explained on the basis of an increase in plasma volume incident to the hydrophilic effect of the circulating acacia

Simultaneous changes in the hematocrit reading and in the plasma protein concentration were measured From these data we have calculated the predicted depression in plasma protein concentration as a result of the increased plasma volume The correlation between the observed and the predicted depression in plasma protein is shown in table 2 This correlation is sufficiently close to indicate that the depression of the plasma protein concentration observed after injection of acacia can be satisfactorily explained on the basis of dilution, which is brought about by the influx of fluid from the edematous tissues into the circulation

The actual plasma volume was measured with congo red in case 8, listed in table 1 The control plasma volume in this case was 2,530 cc Twenty-four hours after the injection of 120 Gm of acacia, this patient's plasma volume was 3,570

TABLE 2—Correlation Between Observed and Predicted Concentration of Plasma Protein

Case	Hematocrit Reading, %		Blood Volume, % Increase *	Plasma Protein, Gm per 100 Cc		
	Control I	After Aenein II		After Aenein		
				Control	Observed	Calculated †
1	33.2	23.8	39.5	4.68	2.81	2.94
2	33.5	23.0	45.6	2.69	1.98	1.60
3	41.9	28.0	48.2	4.34	2.83	2.40
	30.0	37.5	9.0	2.80	2.20	2.48
4	42.5	27.0	57.4	5.03	2.51	2.51
5	42.0	32.5	27.7	3.77	2.35	2.56
6	30.0	26.0	15.4	4.80	3.25	3.94
7	45.0	38.5	19.5	8.3	7.0	6.14
8	23.5	21.0	35.7	4.5	2.5	3.0

\* Hematocrit I — Hematocrit II  
Hematocrit II × 100

† Control Plasma Volume, % × Control Plasma Protein, Gm /100 Cc

Control Plasma Volume, % + Percentage Increase

cc This increase of 38 per cent compares favorably with the 36 per cent increase calculated by the changes in the hematocrit reading Several days later the study was repeated on this patient The control plasma volume was 3,081 cc Twenty-four hours after the injection of 90 Gm of acacia his plasma volume was 3,742 cc This represents an increase of 21 per cent, as compared with an increase of 19 per cent calculated by the changes in the hematocrit reading The clearance of congo red was normal in this patient, 69 per cent of the dye remaining in the plasma at the end of

one hour<sup>13</sup> Several attempts were made to measure the increase in plasma volume by the spectroscopic method using Evans blue Because of the hyperlipemia present in association with the hypoproteinemia, measurement of the plasma volume was unsuccessful by this method

necessary to assume that hepatic damage plays an important role in this depression It is of interest that no patient in our series showed symptoms or signs of hepatomegaly

Successful elimination of edema has been of great value to our patients It has been especially

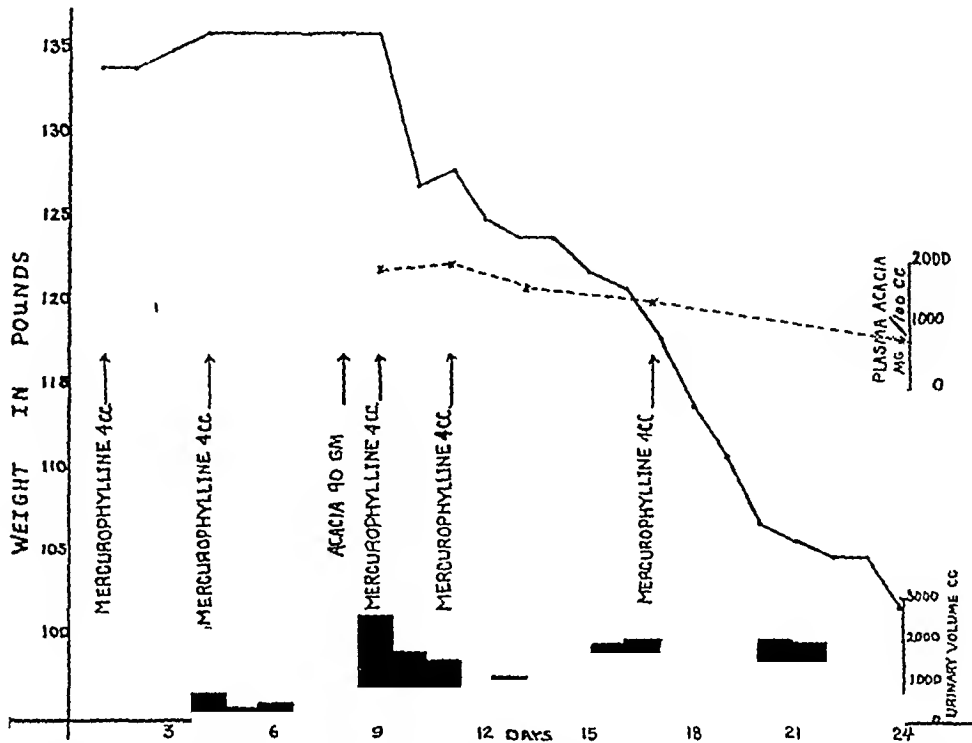


Chart 1—Fluid balance in nephrosis, effects of acacia and mercuriophylline The solid line indicates body weight, the broken line acacia level in the plasma and the solid blocks urinary volume

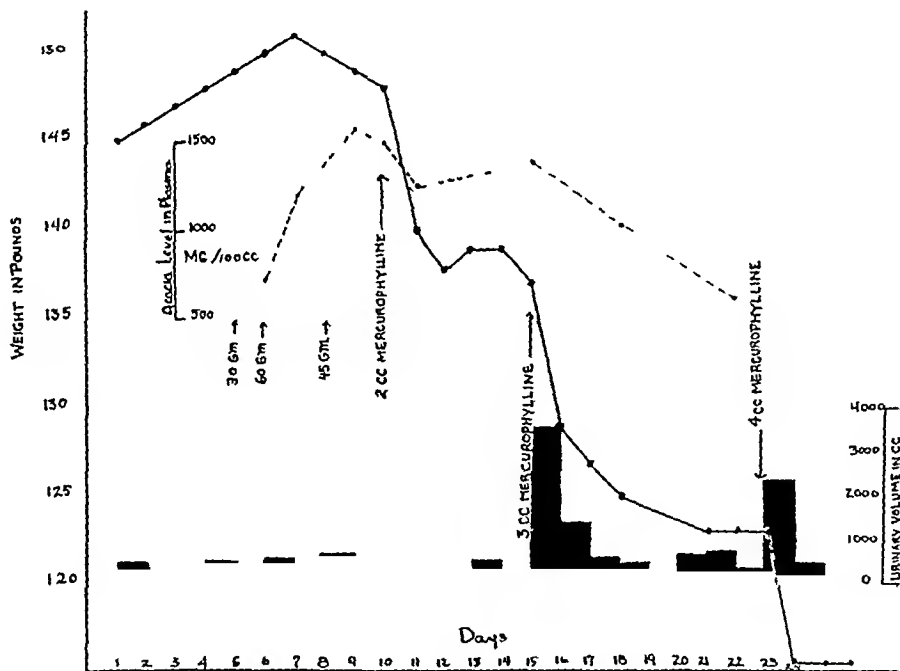


Chart 2—Fluid balance in nephrosis, effects of acacia and mercuriophylline The patient was a woman 25 years old The initial value for total protein was 4.30 Gm per hundred cubic centimeters The solid line indicates body weight, the broken line acacia level in the plasma and the solid blocks urinary volume

Since the increase in plasma volume is sufficient to explain the changes in the plasma protein concentration after injection of acacia, it is un-

valuable to the patients with massive edema, who within from ten days to two weeks are changed from waterlogged, bedridden patients to ambulatory ones, able to return home and resume most of their ordinary daily activities Chart 1 illustrates these results The patient whose course

13 Taran, A, and Eckstein, A Standardization of Congo Red Test for Amyloidosis, *Am J M Sc* 203: 246, 1942

is outlined was a schoolgirl who had been observed for several weeks in the hospital while she was on a regimen of a high protein, low salt diet and restricted intake of fluids. She showed no tendency to lose her edema during this period.

When treatment with acacia and mercuraphylline was started, there was an immediate and progressive loss of edema fluid, so that in fourteen days this patient lost 31 pounds (14 Kg) of water. At that time she became essentially free of edema, although her plasma protein concentration was 3.98 Gm per hundred cubic centimeters. This patient has had no recurrence of edema to the time of this writing, after twelve months' observation.

Chart 2 is another demonstration of the effectiveness of treatment with acacia and mercuraphylline. The patient whose course is described had been treated in the hospital for several months with a high protein, low salt diet and

TABLE 3—Effects of Intravenous Injections of Acacia and Mercuraphylline on Body Weight

Case	Edema	No of Injections	Acacia Dose (Total, Gm)	Period of Treatment	Body Weight Before Acacia, Lb	Body Weight After Acacia, Lb
1 N P (F)	3+	1	120	8 days	113	107
2 M V (F)	4+	6	320	8 wk	169	110
3 V W (F)	3+	3	270	4 wk	99	82
4 M J (M)	4+	1	90	2 wk	136	102
5 T C (M)	No edema	2	180	9 days		
6 A H	3+	3	270	5 wk	146	125
7 I H (M)	1+	1	80	10 days	84	81
8 O G (M)	4+	2	120	3 wk	61	56
9 D D (M)	1+	2	120	3 wk	67	69

with various diuretics, including acidifying salts and mercuraphylline. She was also given large doses of nephritin (a preparation of fresh kidney substance containing hormones thought to be associated with control of renal function and metabolism) without significant reduction of the edema fluid. She lost 38 pounds (17 Kg) of water within sixteen days after the treatment with acacia and mercuraphylline was started. At that time her plasma protein concentration was 3.94 Gm per hundred cubic centimeters. About one month later she again gained about 10 pounds (4.5 Kg) additional edema fluid after an infection of the respiratory tract. She was given two subsequent treatments, after which she became free of edema and remained so.

Table 3 shows the effects of acacia and mercuraphylline on the edema of all the patients in our series. The loss of edema after this treatment was satisfactory in all the adult patients (cases 1 through 6). It appears certain that these patients would not have lost their edema had the acacia not been followed immediately by the mercuraphylline. This fact is demonstrated

in charts 1 and 2. Not only did these patients show no loss in edema, but there was a general tendency for the body weight to increase when acacia alone was administered. This increase occurred in spite of the obvious mobilization of water by the acacia, demonstrated by the reduction in the hematocrit reading. Diuresis was immediate and persistent, however, as soon as the mercuraphylline was given. That the mercuraphylline alone was not the effective agent was demonstrated by the administration of mercuraphylline before acacia was given.

Mercuraphylline alone usually resulted in a moderate diuresis, but there was no persistent loss of weight. A typical example is seen in chart 1. Here it is seen that the total effect of the mercuraphylline alone was a slight gain in body weight. It appears, therefore, that even though acacia mobilizes fluid, thus increasing the plasma volume, a stimulus to renal excretion is necessary in order to effect diuresis.

The lack of improvement of the 3 children studied, as contrasted with improvement of the adults, was striking. I. H. and C. G. (cases 7 and 8) had little edema initially. A slight loss of edema occurred in these patients, but a recurrence of edema developed after their discharge from the hospital. D. D. (case 9) showed not even temporary loss of edema, even though his edema and ascites were massive.

Since this paper was submitted for publication, 1 other patient has been studied. She is a 14 year old girl. Six weeks prior to her hospitalization, generalized edema and massive proteinuria developed. At the time of her admission, her plasma protein concentration was 4.1 Gm per hundred cubic centimeters. She was treated with a high protein, low salt diet. During the course of thirty days she was given a total of 4 liters of whole blood and 25 Gm of serum albumin in an attempt to raise the plasma proteins and reduce the edema. As can be seen from chart 3, there was a progressive increase in body weight.

Her edema and ascites became extreme. Within a period of five days after treatment with acacia and mercuraphylline was started, this patient lost 29 pounds (13 Kg) of water, and she has been free of edema to the time of this writing. The proteinuria has continued.

The plasma acacia was measured for all patients. In general, the percentage of increase in plasma volume was proportional to the quantity of acacia injected per kilogram of body weight. As seen in table 1, the plasma acacia varied from 1 to 2.7 Gm per hundred cubic centimeters. There was a gradual decrease in the plasma acacia after the first two days. However, small quantities of acacia were still demonstrable in

the plasma for several months after the last administration

*The Urinary Excretion of Acacia*—The excretion of acacia in the urine was determined for most of our patients. By some, measurable amounts of acacia were continuously excreted twenty to thirty days after the last injection. From 1 patient 38 per cent of the 135 Gm injected was recovered in the urine in a thirty day collection period. The fact that on the average about 1 Gm per day was still being recovered at the end of the collection period suggests that a much larger percentage of acacia might have been recovered had the period of collection been extended.

On the other hand, 1 of the patients most severely ill showed a progressive decrease in the urinary excretion of acacia during a collection

a given patient, however, was relatively uniform. Comparison of the total protein excreted in the urine in four day periods showed no consistent changes in the control period or in the period during which mercuriophylline and acacia were administered.

*Complications of Acacia Therapy*—The most common complications of the treatment were a mild fever and, occasionally, a chill. Some of the patients vomited several times after the injection was completed. This type of reaction was minimized and sometimes apparently prevented by the administration of acetylsalicylic acid and ephedrine when the treatment was started.

In 1 patient (case 3) epistaxis developed after treatment on two occasions. At the time of the epistaxis his prothrombin time was 58 per cent of normal. The epistaxis stopped

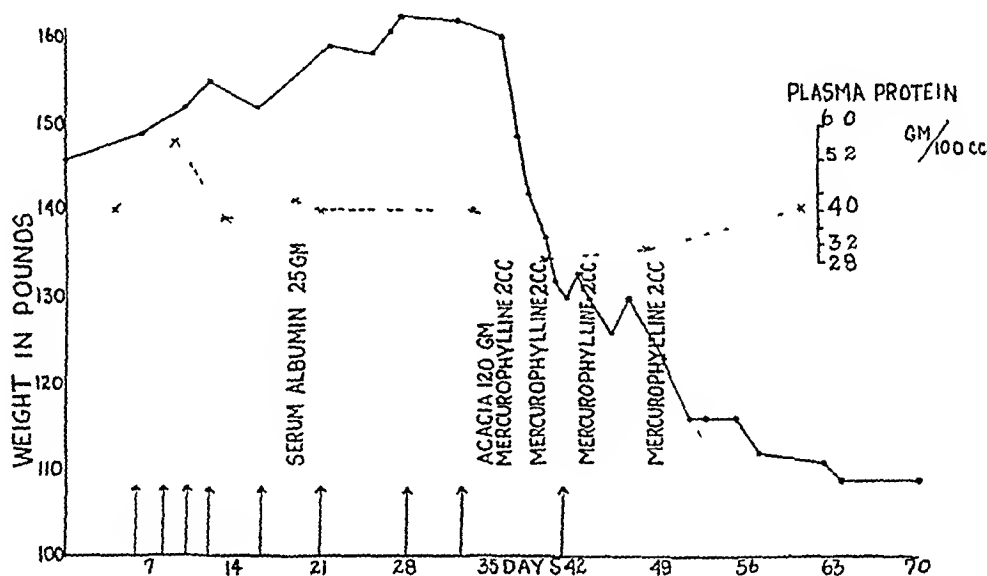


Chart 3—Fluid balance in nephrosis, effects of blood transfusions, mercuriophylline and acacia. The solid line indicates body weight, each long arrow indicates a transfusion of 500 cc of whole blood, and the broken line indicates the total plasma protein concentration.

period of fifteen days, so that after twelve days no acacia was found in the urine for the remainder of the period. For both of the patients cited the clinical results were excellent. In neither was there a parallel change in the urinary excretion

TABLE 4—Urinary Excretion of Acacia After Intravenous Injection

Case	Acacia Injected, Gm	Acacia Recovered, Gm	Recovery, Percentage	Period of Collection, Days
M V	135	50.8	38	30
J W	90	10.9	12	12
M J	90	12.6	14	15
I H	80	8.8	11	11
W C	120	6.6	5.5	10

of protein. Table 4 summarizes the data on the urinary excretion of acacia.

The degree of proteinuria varied considerably among the patients studied. The magnitude for

shortly after the intramuscular administration of a synthetic vitamin K preparation<sup>13a</sup>. The prothrombin time showed a drop of 10 per cent to 25 per cent in several other patients for whom this determination was made before and after injection of acacia. However, there were no hemorrhagic manifestations in any of the other patients. These were the only complications observed during the course of these experiments.

*Distribution of Acacia in Body Tissues*—One patient who had hypoproteinemia and edema as a complication of a chronic inflammatory effusion of the pleural and peritoneal cavities was treated with acacia. He died fifty days after the injection of 120 Gm of acacia. The distribution of

13a The preparation used was Synkayvite, a water-soluble naphthohydroquinone with pronounced vitamin K activity, the sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

acacia found in his tissues and bile are listed in table 5

## COMMENT

That acacia is a useful drug in the treatment of resistant nephrotic edema seems unquestionable. The major objection to acacia, namely, its effect on the plasma proteins and on the liver, bears careful analysis. There seems no doubt that

TABLE 5—*Distribution of Acacia in Body Tissues (Fifty) Days After Intravenous Injection*

Tissues	Concen- tration, Percentage	Weight of Organ, Gm	Total Acacia, Gm
Brain	0	1,275	0
Heart	0.093	225	0.20
Stomach	0.234	?	?
Lung	0.335	900	3.19
Kidney	0.516	300	2.01
Liver	2.070	1,200	24.80
Spleen	5.450	150	8.17
Blood	0.846		
Bile	0.218		
Total recovery			33.37

if sufficiently large doses of acacia are administered they may produce undesirable effects. The same is true, however, of almost any drug. The rapidity with which the plasma protein concentration drops after injection of acacia seems to eliminate damage to the liver as its primary cause. Other forms of acute hepatic damage do not cause such rapid depression in protein concentration. When these facts are considered in connection with the decided increase in plasma volume incident to injection of acacia, it seems almost certain that this depression in plasma protein is primarily the result of dilution. The point of view that acacia in the liver inhibits

TABLE 6—*Regeneration of Plasma Proteins After Acacia*

Date	Plasma Protein, Gm per 100 Cc	Albumin Globulin	Plasma Acacia, Mg per 100 Cc
8/20/43	2.37	0.30	1,618
8/24/43	3.16	0.91	1,326
8/31/43	3.98	0.63	853
9/11/43	4.93	0.81	
10/ 2/43	5.50	1.05	
11/ 2/43	6.53	1.72	

regeneration of plasma protein has not been established. The fact that in some nephritic patients plasma proteins are not built up to normal levels for many weeks after acacia therapy cannot be admitted as proof, since one often can make the same observation concerning nephritic patients who have never received acacia therapy. Further, in some patients plasma proteins are regenerated rapidly even after acacia therapy

Such an example is illustrated by table 6, concerning V W (case 3 in our series).

It is of interest to note the quantities of acacia given in the reported experiments in which patients were found to have enlarged tender livers and in the experiments on dogs in which the livers were four to five times normal size. The patient reported by Faulkenstein and Jackson<sup>2b</sup> received 705 Gm of acacia, which was equivalent to 24.5 Gm per kilogram of body weight. In the experiments on dogs reported by Yulie and Knutti,<sup>31</sup> the animals received from 28 to 41 Gm of acacia per kilogram of body weight. The quantity of acacia given in our series varied from 1.45 to 5.94 Gm per kilogram, with an average of 3.18 Gm per kilogram of body weight. There seems to be no necessity for the administration of such enormous quantities of acacia as 20 to 40 Gm per kilogram of body weight in the treatment of nephrotic edema. If 1 or 2 Gm of acacia per kilogram are injected one should obtain a significant increase in the plasma volume. A diuretic such as mercurophylline should then be administered. This procedure can be repeated several times if necessary. If no persistent reduction in the edema fluid occurs after that amount of acacia, there appears to be no assurance that further acacia therapy will be beneficial.

Some of the failures of acacia therapy in nephrotic edema reported in the literature were undoubtedly due to the fact that the mobilization of water by acacia was not a sufficient stimulus in itself to cause diuresis. This fact was repeatedly demonstrated in our experiments. The reason for this result is not clear. Although the nephrotic kidney handles chloride essentially in the same way as does the normal one,<sup>14</sup> the exact relation between renal damage in glomerulonephritis and retention of salt and water is still obscure.<sup>15</sup> The edema fluid in persons with nephrosis is essentially a colloid-free filtrate of plasma.<sup>16</sup> As acacia mobilizes this edema fluid thus increasing the plasma volume, it appears certain that the associated sodium is simultaneously mobilized and presented to the kidney. However, because of the composition of the edema fluid, there need be no change in the concentration of sodium and chloride in the plasma after acacia is administered. It may be true that

14 Loeb, R. F., Atchley, D. W., Richards, D. W. Jr., Benedict, E. M., and Driscoll, M. E. On the Mechanism of Nephrotic Edema, *J. Clin. Investigation* **11** 621, 1932.

15 Peters, J. P., Salt and Water Metabolism in Nephritis, *Medicine* **11** 435, 1932.

16 Loeb and others<sup>14</sup> Peters<sup>15</sup>

the blood volume in patients with nephrotic edema is more nearly normal after mobilization of water by acacia than before, so that hypervolemia need not actually occur. In this event an additional stimulus such as mercuriophylline might be necessary for diuresis. Decreased blood volume in patients with stabilized or increasing nephrotic edema has been reported as characteristic.<sup>17</sup> The patients in this series for whom the blood volume was measured showed values as much as 24 per cent below that expected for their ideal weight (Gibson and Evans)<sup>18</sup>.

The ineffectiveness of acacia and mercuriophylline in the treatment of nephrotic children as contrasted with the effectiveness in treatment of nephrotic adults in this group of patients is unexplained.

#### CONCLUSIONS

The clinical and physiologic effects of the intravenous injection of acacia have been studied on 8 patients with the nephrotic syndrome of chronic

17 Waterfield, R. L. Changes in Blood Volume in Patients with Edema of Renal Origin, *J Clin Investigation* 9 589, 1931. McClure, W. B., de Takáts, C. B., and Hinman, W. F. Mechanism of Edema of the Renal Type, *Arch Int Med* 51 819 (June) 1933.

18 Gibson, J. G., and Evans, W. A. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, *J Clin Investigation* 16 317, 1937.

glomerular nephritis, on 1 patient with hyperproteinemia and on 1 patient with hypoproteinemia and edema complicating a chronic polyserositis.

A simultaneous reduction in the plasma protein concentration and in the hematocrit reading was constantly observed after the injection of acacia. By means of the changes in the hematocrit reading, the degree of depression of the plasma protein concentration was predicted. This predicted depression showed close correlation with the observed depression. The reduction in plasma protein concentration, therefore, is considered to be primarily the result of an increase in plasma volume at the expense of the edema fluid, incident to the hydrophilic effect of the circulating acacia.

No evidence was found to indicate that the injected acacia inhibited regeneration of plasma protein. No serious complications were observed.

Concentrations of acacia in the tissues of 1 patient who died fifty days after injection of acacia were studied. The greatest concentrations were found in the liver and in the spleen.

No beneficial effect was observed from the use of this therapy on the children studied in this series.

Intravenous injections of acacia, when followed by mercuriophylline injection, proved a valuable aid in eliminating nephrotic edema in the adult patients studied.

# RECURRENT MENINGOENCEPHALITIS DUE TO THE VIRUS OF LYMPHOGRANULOMA VENEREUM

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The concept of lymphogranuloma venereum as a systemic infection rather than a local one is of fairly recent origin. Beginning with the report of Durant, Nicholas and Favre<sup>1</sup> in 1913, evidence has accumulated in support of this view. Van Rooyen and Rhodes<sup>2</sup> stated that, in addition to the more frequent involvement of genitalia and regional lymph glands, lymphogranuloma venereum may manifest itself by involvement of the throat, with inflammation of the tonsils, ulcerations or angina, by fever, with headaches and other pyrexial disturbances, by cutaneous rashes, by various forms of articular involvement, by generalized involvement of the lymph nodes, with splenomegaly and hepatomegaly, by granulomatous conjunctivitis, by epididymitis and by meningoencephalitis. In 1936 von Haam and D'Aunoy<sup>3</sup> reported the isolation of the virus from the spinal fluid of 2 patients during the acute stage of the infection, when the cerebral manifestations consisted mainly of headaches. Rajam<sup>4</sup> reported a case of lymphogranuloma venereum in which death from meningoencephalitis occurred after surgical intervention on the buboes. Sabin and Aring<sup>5</sup> isolated the virus from the spinal fluid of a patient showing pronounced cerebral changes and also from the inguinal lymph node six weeks after the onset of the acute phase of

the illness. They also found further proof, in complement fixation studies, of the etiologic relation of the virus to the illness encountered. Zarafonitis<sup>6</sup> published a report of 2 cases, in 1 of which the virus was isolated from the inguinal lymph node five months after the onset of the illness and the serum was found to fix the complement. Of interest in this case, also, was the colloidal gold curve, which showed a persistent, strongly positive first zone reaction.

In the case to be presented in this paper an attempt was made to isolate the virus from blood, from spinal fluid and from the originally involved inguinal lymph nodes. Numerous serial intracerebral passages in mice were tried with both the spinal fluid and the blood but without success in recovering the virus. The specimen of serum, however, was found to fix the complement in significant dilution with lymphogranuloma venereum antigen as well as with psittacosis antigen, and fixation of complement was also obtained with spinal fluid. Also of interest in this case is the colloidal gold curve which is similar to that shown in the case reported by Zarafonitis<sup>6</sup>, that is, there is a strongly positive first zone reaction.

## REPORT OF A CASE

V P, a 21 year old white man, was admitted to the United States Marine Hospital Chicago, on Aug 9, 1944, with the chief complaint of "double vision". At that time he stated he had been in good health until January, when bilateral buboes developed. These were incised, and he was given sulfonamide compounds, with an apparently uneventful recovery. In April, after he had had sexual contact with a "dark-skinned" Puerto Rican girl, swelling of the inguinal lymph nodes again developed bilaterally. This was followed within a week to ten days by the gradual development of headache and malaise followed by chilly sensations and fever. The headache became progressively more severe, and he noticed twitching of the muscles of his face. On May 9 he was admitted to the United States Marine Hospital, Boston. Physical examination at that time

6 Zarafonitis, C J D. Meningoencephalitis in Lymphogranuloma Venereum, *New England J Med* 230 567-573, 1944

1 Durant, Nicholas and Favre. Lymphogranulomatose inguinale subaigue, d'origine genitale probable, peut-etre venerienne, *Bull Soc med d'hop Universitaires de Quebec* 35 274-288, 1913

2 Van Rooyen, C E, and Rhodes, A J. *Virus Diseases of Man*, London, Oxford University Press, 1940, pp 176-196

3 von Haam, E, and D'Aunoy, R. Infectivity of Spinal Fluid in Lymphogranuloma Inguinale, *J A M A* 106 1642-1643 (May 9) 1936

4 Rajam, R V. Report of Fatal Case of Lymphogranuloma Inguinale from Meningoencephalitis, *Brit J Ven Dis* 12 237-241, 1936

5 Sabin, A B, and Aring, C D. Meningoencephalitis in Man Caused by Virus of Lymphogranuloma Venereum, *J A M A* 120 1376-1381 (Dec 26) 1942

showed twitching of the muscles of the entire face, a few small palpable lymph nodes in the neck, bilateral inguinal scars from previous buboes and, on either side, a firm inguinal lymph node about the size of a hickory nut. There were no penile lesions. There was no stiffness of the neck and no Kernig sign. A tentative diagnosis of meningococcic meningitis was made. The spinal fluid showed 250 cells, mostly lymphocytes, the pressure was 150 mm of water and the fluid clear. Culture of the spinal fluid showed no growth. Values for proteins and chlorides in the spinal fluid were normal.

TABLE 1—Summary of Results of Examinations of the Spinal Fluid During June 1944

	6/5/44	6/11/44	6/15/44	6/21/44	6/24/44
Color	Color less	Color less	Color less	Color less	Color less
Turbidity	Clear		Clear	Clear	
Protein (Mg /100 Cc)	44	80	38	52	
Sugar (Mg /100 Cc)	40	47	50	60	50
Cell count	270	166	62	40	55
Polymorphonuclear leukocytes	70	25	0	0	12
Mononuclear leukocytes	30	70	100	100	88
Rytz reaction	Negative				
Wassermann reaction	Negative				
Colloidal gold curve	Negative				
Red blood cells	0				
Growth in culture	None	None	None	None	None
Growth in smear	None	None	None		None

Results of urinalysis and of studies of the blood during this same time were essentially normal. Wassermann and Kline reactions of the blood were negative.

Wassermann and Davies-Hinton reactions of the blood were negative. Culture of the blood showed no growth. The Frei test elicited a positive reaction. The blood count was essentially normal. Under treatment with sulfadiazine, the temperature returned to normal within three days. However, there were several recurrences of fever during his stay in the hospital. At the time of his discharge on May 29, he appeared to have recovered.

After leaving the Boston Marine Hospital, the patient went to Minneapolis, where on June 5 there was a recurrence of the intense headache and vomiting. He entered a hospital on that date, and a diagnosis was made of recurrent meningococcic meningitis, based on clinical findings. Numerous spinal taps were performed, the results of which, along with other laboratory data, are summarized in table 1.

He was again treated with sulfonamide drugs and became asymptomatic and was discharged on June 26. He had remained at home about one week when a stiff neck, headache and vomiting developed and he was hospitalized at another hospital, where he was again given a course of sulfonamide drugs, with prompt symptomatic recovery. One week later he had a similar attack and returned to the hospital. His complaints on this admission were intermittent headaches and stiffness in the back of his neck and in his back. He was said at times to become noisy, moaning and crying. It was reported by the eye, ear, nose and throat consultant that the patient had an involvement of the third cranial nerve, with diplopia, and some bilateral papilledema. Results of examination of the spinal fluid were reported as follows: Kline reaction positive (2 plus),

Kolmer-Wassermann reaction negative, Nonne reaction positive, fluid cloudy, smear negative for bacteria, cells 6 and colloidal gold curve 5555543211. He again became asymptomatic after the administration of sulfonamide drugs and was discharged to report to the United States Marine Hospital, Chicago, for further observation and treatment.

Physical examination at the time of his admission to the Chicago Marine Hospital showed the head to be normal. The pupils were equal and regular and reacted to light and in accommodation, the scleras were clear, there was no demonstrable muscular imbalance and no nystagmus or lid lag, and the fundi appeared to be within normal limits. The neck was freely flexible. No enlarged nodes were noted. There were bilateral inguinal scars with small hard inguinal lymph nodes palpable bilaterally. Reflexes and other neurologic signs were normal throughout, with the exception of a questionable Babinski reflex on the right. There was noted a slight hesitancy of speech, which the patient stated had not been present prior to his illness. Laboratory studies showed normal urine. There were 5,100,000 red blood cells, 14.6 Gm of hemoglobin, 5,600 white cells, 38 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils, 50 per cent neutrophils and 5 per cent stab forms. The Wassermann and Kahn reactions of the blood for syphilis were negative. In the blood, the total protein was 7.15 Gm per hundred cubic centimeters, albumin 3.6 Gm and globulin 3.5 Gm. Cultures of nasopharyngeal materials showed no growth of meningococci. A spinal puncture performed on August 12 revealed a total cell count of 91, with 96 per cent monocytes and 4 per cent polymorphonuclear leukocytes. The Pandy reaction was positive (4 plus). Culture of the spinal fluid showed no growth, and the Kahn and the quantitative Kolmer-Wassermann reactions were negative in all dilutions. The total protein was 156 mg per hundred cubic centimeters, chlorides 620 mg and sugar 60 mg, and the colloidal gold curve was 5555543100. On August 26 a second spinal puncture was done, and the report showed a 4 plus Pandy reaction, a cell count of 4,

TABLE 2—Summary of Results of Examinations of the Spinal Fluid in Chicago Marine Hospital

	8/11/44	8/26/44	11/17/44
Cell count	96% Mononuclear leukocytes, 4% polymorphonuclear leukocytes	4 Mononuclear leukocytes	0
Pandy reaction	4 plus	4 plus	Trace
Growth in smear	None		None
Growth in culture	None		None
Kahn reaction	Negative		
Quantitative Kolmer-Wassermann reaction	Negative	Negative	Negative
Total protein	156 mg /100 cc	61 mg /100 cc	
Chlorides	620 mg /100 cc		
Sugar	60 mg /100 cc		
Colloidal gold curve	5555543100	5543510000	554211000

with monocytes predominating, a negative quantitative Kolmer reaction, 61 mg of total protein and a colloidal gold curve of 5543510000. A specimen of this fluid, together with a sample of blood, was sent to Dr. John L. White at the laboratory of the Chicago Health Department for complement fixation tests for lymphogranuloma venereum. The complement was fixed with both the blood and the spinal fluid. The Frei test elicited a 1 plus positive reaction, but the control test

showed a positive reaction of about the same degree. The results of the tests made at this time are summarized in table 2.

On August 29 the patient suffered a recurrence of his former symptoms, complaining of severe headache, diplopia, stiff neck and vomiting. Treatment with sulfadiazine was started, with prompt symptomatic improvement. The drug was continued at the rate of 1 Gm every four hours, day and night, for a period of one week and then four times a day for five weeks.

On September 2 specimens of blood, serum and spinal fluid were submitted to the National Institute of Health for virus and complement fixation studies. The virus was not isolated. Complement fixation was confirmatory. A second specimen of spinal fluid was sent to Dr. White at the Chicago Health Department on October 23, and again a complement fixation for lymphogranuloma venereum was reported. Efforts to isolate the virus from the excised inguinal lymph node were unsuccessful. Microscopic studies of this node showed a chronic, nonspecific fibrous lymphadenitis.

On October 25 the patient, at that time being entirely asymptomatic, was discharged to the status of an outpatient. He was seen again on November 14, when he stated that he felt entirely well and had had no recurrences of any sort. A spinal puncture was performed on that date, and the report was as follows: The quantitative Kolmer reaction was negative in all dilutions, no cells were found, there was a trace of a Pandy reaction, and the colloidal gold curve was 5542211000.

#### COMMENT

A review of the literature reveals 6 previously reported cases of meningoencephalitis presumably due to the virus of lymphogranuloma venereum. The virus itself was isolated in 4 of these cases—in 3 from the spinal fluid and in 1 from an inguinal lymph node only. Further confirmation was obtained in 2 of these cases by complement fixation studies of the serum.

In the case presented in this paper the virus was not isolated. This failure to isolate the virus may have been due in part to the length of time elapsed before this study was attempted and also to the considerable amount of treatment with the sulfonamide drugs which this man had previously received. Virus studies were performed by Dr. Donald J. Davis, of the National Institute of Health, Bethesda, Md. Dr. Davis reported that numerous serial intracerebral passages in mice were tried with both the spinal fluid and the blood but without the recovery of any specific virus. The specimen of serum, however, showed complement fixation in significant dilution with lymphogranuloma venereum antigen, as well as with psittacosis antigen.

The report of the microscopic examination of the excised inguinal lymph node stated that the capsule was thickened and fibrosed. Fibrous bands extended from the capsule and penetrated into the cortex. Within the medulla there were

also thick fibrous deposits. The follicles were obvious and were composed primarily of small lymphocytes. Reticulum cells were relatively sparse. Fibroblastic activity in the follicles was present within the medulla. Reticulum cells were increased in number. Blood vessels were thickened. No indications remained that there was a specific infection.

Isolation and identification of the virus is too elaborate and slow a procedure to use routinely for diagnostic purposes. It is necessary, therefore, to depend on some other procedure for laboratory confirmation. The complement fixation test thus becomes a valuable aid in early diagnosis of infections with the virus of the lymphogranuloma-psittacosis group. Differentiation between these conditions must depend on clinical observations, since with the antigens now available it is not possible to differentiate these closely related viruses. Employment of the complement fixation test on spinal fluid in this condition has not previously been reported, and this study was facilitated by the use of this procedure by Dr. John L. White, of the laboratories of the Chicago Health Department.

The value of the Frei test as a diagnostic aid is questionable. Although the original test performed in Boston was reported to have elicited a positive reaction, a subsequent test in this hospital was doubtful, and there have been many instances of negative reactions to Frei tests in which the clinical evidence was overwhelmingly in favor of lymphogranuloma venereum. In the case reported by Zarafonitis,<sup>6</sup> the reaction to the Frei test was negative at the time the virus was recovered from an excised lymph node, although it subsequently became positive.

The results of examinations of the spinal fluid in this case are of interest, but, with the exception of the complement fixation, not diagnostically specific. The colloidal gold curve was persistently of the first zone, dementia paralytica type and the total protein was slightly increased (156 mg per hundred cubic centimeters). These observations resemble those in the case reported by Zarafonitis,<sup>6</sup> but the values are less extreme. For one specimen the Kline reaction was reported 2 plus positive, but for all subsequent specimens this, as well as all other reactions for syphilis, was negative.

The response of this condition to sulfonamide therapy appeared to be satisfactory. With each of his attacks the patient promptly became asymptomatic on institution of this treatment. The recurrences are believed due to the fact that the drug was not continued over a long enough period. After a course of treatment with sulfa-

diazine lasting approximately six weeks the patient was apparently entirely recovered. It would appear from this case, therefore, that rather prolonged sulfonamide therapy is necessary to effect a cure in this condition.

#### SUMMARY

A review of the literature presented evidence that the virus of lymphogranuloma venereum can act as the causative agent in meningoencephalitis.

A case of meningoencephalitis with evidence incriminating this virus as the probable cause was observed.

The value of various laboratory procedures as diagnostic aids was considered.

Treatment with the sulfonamide drugs was found to be effective but must be continued for a considerable period after the patient becomes asymptomatic to prevent recurrence.

## Book Reviews

**Clinical Heart Disease** By Samuel A. Levine, M.D., F.A.C.P. Third edition. Price, \$6. Pp 462, with 157 illustrations. Philadelphia: W.B. Saunders Company, 1945.

The appearance of the third edition of this popular book is welcome indeed, for it continues to fulfil the need for a simple, readable account of the common problems of heart disease. Its style is forceful and expresses the experiences and convictions of the author. It demonstrates the qualities that have made him so excellent a clinical teacher. The sections on the surgical treatment of patent ductus arteriosus and on the chemotherapy, including treatment with penicillin, of subacute bacterial endocarditis have been amplified. A summary of studies on the heart in scleroderma, on rupture of valves and on the heart in Addison's disease has been added. The section on electrocardiography has been expanded greatly, and special reference has been made to the precordial leads. It is apparent that the author has followed the views of Wilson and his school closely in the latter development, and at times the reviewer feels that the subject has been made more complex than necessary for the average practitioner, for whom this book is intended. The section on the arrhythmias continues to be lucid and valuable. The discussion of phonocardiology is unnecessarily complex for the ordinary reader, and there is little purpose in illustrating the cardiac sound tracings.

The author is at his best when he is describing the clinical picture and the management of heart disease, drawing on his extensive experience. He is less so when he delves into the genesis and physiologic disturbances associated with these diseases. There are many statements in this category with which the reviewer cannot agree.

This book is an outstanding contribution to the literature concerning heart disease, which no physician interested in the subject can afford to overlook.

**Doctors at War** Edited by Morris Fishbein, M.D. Price, \$5. Pp xiii + 418, with 82 illustrations. New York: E.P. Dutton & Co., Inc., 1945.

This book has been written by sixteen experts under the editorial leadership of one. It describes doctors at war and how their different talents have been amalgamated for the benefit of the nation.

The contents are particularly well organized and comprehensive. There are chapters which outline the medical side of Selective Service, procurement and assignment, the practice of preventive medicine in the

army and the accomplishments of the United States Public Health Service. There are chapters which tell what the doctor in active service actually does in different theaters of operation when he is an officer in the army, navy or air forces. There is a chapter which discusses the problem of convalescence and rehabilitation and another which deals with the Veterans' Administration. There are chapters which sketch the work of the Red Cross in making blood substances available to the wounded and how investigations were carried out under the National Research Council.

One of the most interesting features is the manner in which the different chapters are written. Each one is like a presentation to a medical society, restrained, unemotional, clear and factual. Yet any one reading between the lines feels the strength of American medicine, its ideals and its unselfishness.

The volume is an important one. All physicians will take pride in such an historic document.

**Patients Have Families** By Henry B. Richardson, M.D., F.A.C.P., associate professor of clinical medicine, Cornell University Medical College, attending physician, New York Hospital, visiting physician, Bellevue Hospital. Cloth. Price, \$3. Pp 408. New York City: The Commonwealth Fund, 1945.

This work is another of the excellent contributions of the Commonwealth Fund and represents the recognition of a hitherto neglected difficulty. It deals with the effect of the patient's illness on his family. It describes the effect of the family and the environment on the illness of the patient. It points out the proper attitude of the physician and the psychiatrist in the solution of the problem. The medical social worker is given a place in the picture. The author points out the opportunity for research in the study of the family unit, and he gives numerous examples of professional technics to be used in meeting the problems.

It seems obvious that this book must produce a variety of reactions in its readers. By the social worker, the psychologist and the highly specialized psychiatrist the book will doubtless be received as the finger that points toward the proper solution of the problem. To many less sympathetic readers, the method will seem to perpetuate and worsen a condition that has grown out of a too restricted medical interest.

At any rate, the book plainly points out that the medical profession is confronted with a situation that it may well have created and which must be met. Whether the author's method of meeting it is the correct one remains for the future to decide.

# Progress in Internal Medicine

## INFECTIOUS DISEASES

ELEVENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

HOBART A. REIMANN, M.D.

PHILADELPHIA

(Concluded from Page 129)

### DISEASES OF THE GASTROINTESTINAL TRACT

*Epidemic Nausea, Vomiting and Diarrhea (Viral or Viroid Dysentery?)*—Report is made<sup>146</sup> of a widespread mild contagious disease characterized by symptoms of a deranged gastrointestinal tract. For several reasons the disease has not attracted much medical attention. First, like the common cold, it is mild and its victims are usually ambulatory; second, its manifestations are not so obvious as those of the cold, and, third, the symptoms, because of their nature, are usually not discussed in casual conversation. It is probably worldwide in distribution, and its mode of dissemination suggests the cause to be a filtrable agent which passes from person to person as in air-borne infections. In tests made on volunteers who inhaled filtrates of garglings and of stools, presumptive evidence was obtained that the causative agent is filtrable and is air-borne, but the experiments were made with fresh material, by necessity during an epidemic period, so that final proof is still needed.<sup>147</sup> The mere absence of a demonstrable bacterial cause does not prove that a virus is the cause. The etiologic problem at present is as unsettled as that of viroid, or viral, pneumonia, and the matter of naming the disease is similarly confused. It can hardly be called gastroenteritis without evidence of actual inflammation of the tract. The name "epidemic nausea, vomiting and diarrhea" is not wholly satisfactory either, it is cumbersome, and one or two of the named symptoms may be absent in different patients. The term "viral, or viroid, dysentery" is presented for consideration. The word "dysentery" appropriately means difficulty with the bowel, and "viral or viroid" suggests a filtrable virus as the cause. The disease would thus take its

place among the infectious diseases called bacillary dysentery and amebic dysentery.

Incidentally, Rosenow, in his usual manner,<sup>148</sup> obscures the issue by introducing a streptococcus "having special affinity for the gastrointestinal tract" which in its filtrable form causes the disease.

*Epidemic Jaundice, Infectious Hepatitis*—Epidemic jaundice, or infectious hepatitis, is called one of the new epidemic diseases of the current war. It has indeed been a serious problem, so much so as to interfere at times with military operations.<sup>149</sup> The problem of its identity with various other forms, namely, vaccine jaundice or homologous serum jaundice, arsenotherapy jaundice and others, is still unsettled because of their clinical and pathologic similarities. The chief difference is in the length of the incubation period, but, according to Oliphant,<sup>149</sup> patients who recovered from serum jaundice are immune to inoculation with serum from patients with infectious hepatitis or with icterogenic yellow fever vaccine, suggesting the identity of these diseases. Immunity lasts twelve to eighteen months. MacCallum<sup>150</sup> noted jaundice in volunteers receiving injections of serum from patients who had postarsenotherapy jaundice. According to Havens,<sup>151</sup> the icterogenic agent of infectious hepatitis can be transmitted in serial passage in human volunteers. The agent, like that of post-vaccinal jaundice and homologous serum jaundice, is durable and survives heat at 56 C for

146 Reimann, H. A., Hodges, J. H., and Price, A. H. Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, *J. A. M. A.* **127** 1-5 (Jan 6) 1945.

147 Reimann, H. A., Price, A. H., and Hodges, J. H. The Cause of Epidemic Nausea, Vomiting and Diarrhea (Viral Dysentery?), *Proc. Soc. Exper. Biol. & Med.* **59** 8-9 (May) 1945.

148 Rosenow, E. C. Infectious Gastroenteritis. An Epidemiologic and Laboratory Study, *Am. J. Digest. Dis.* **11** 381-391 (Dec) 1944.

149 Oliphant, J. W. Infectious Hepatitis. Experimental Study of Immunity, *Pub. Health Rep.* **59** 1614-1616 (Dec 15) 1944.

150 MacCallum, F. O. Transmission of Arsenotherapy Jaundice by Blood. Failure with Feces and Nasopharyngeal Washings, *Lancet* **1** 342 (March 17) 1945.

151 Havens, W. P. Properties of the Etiologic Agent of Infectious Hepatitis, *Proc. Soc. Exper. Biol. & Med.* **58** 203-204 (March) 1945.

thirty minutes. The same author and others<sup>152</sup> show that the virus is present in the blood, feces, nasopharyngeal washings and urine in the early stages and even before clinical symptoms appear. The latter point is reemphasized by Neefe and his associates,<sup>153</sup> who also report on several patients in whom clinical jaundice never appeared and for whom the diagnosis would have been missed had not laboratory evidence of hepatic dysfunction been obtained. One third of the victims of one epidemic did not become jaundiced.<sup>154</sup>

The mortality rate is generally believed to be about 0.2 per cent, but in a certain small percentage of cases there is evidence of residual injury to the liver. In a study on 200 patients<sup>155</sup> who still were not well five to nine months after the original attack, most of them were found to have symptoms which could be ascribed to neurosis, but about 12 per cent had evidence of persistent hepatic disease.

Treatment of jaundice with methionine was unsuccessful,<sup>156</sup> but experiences with gamma globulin were encouraging.<sup>154</sup> In one epidemic the incidence of hepatitis was said to have been significantly reduced by the intramuscular injection of gamma globulin in persons exposed to the infection. The substance seemed to prevent or ameliorate the disease if given during the incubation period.

*Shigellosis*—In continued studies on acute diarrheal diseases, Hardy and Watt<sup>157</sup> reempha-

size the great preponderance of mild attacks of simple diarrhea over so-called typical cases of bacillary dysentery. The number of cases of mild diarrhea is usually difficult to determine, since mild attacks are quickly forgotten. About 9 convalescent or passive carriers were found for each recognized case. In most instances the source of infection cannot be found.

Some order at last seems to be coming out of the classification of this group of bacteria, after the early work of Andrewes, Inman and Boyd and now after that of Weil and his associates.<sup>158</sup> In the *Shigella paradysenteriae* (Flexner) group there are eighteen patterns of agglutinative behavior, divided now into fourteen types with a single primary antigen and four with dual primary antigens.

Morton and Engley<sup>159</sup> critically review the evidence both favoring and discrediting the value of bacteriophage in the treatment of bacillary dysentery. Most clinical reports thus far published are inconclusive, but trial in animals seems to show its unmistakable therapeutic effectiveness. If either the sulfonamide compounds or streptomycin proves to be more effective, there will be no need for the use of bacteriophage or for immunotherapy.

In an attempt to provide a reliable method of prophylactic immunization, volunteers were given injections of a specific polysaccharide antigen of Flexner dysentery bacilli.<sup>160</sup> Agglutinins developed in the blood for the homologous strain and for other groups as well. The blood also contained protective antibodies. On the other hand, in a different study,<sup>161</sup> the agglutination test as usually performed was found to be an unreliable means of diagnosing infections with various members of the *Shigella* group, nor was it an index of immunity or susceptibility to infection. The agglutinin titer was usually higher for patients who shed bacilli in their feces but not sufficiently high, nor consistently so, to permit interpretation in individual cases.

158 Weil, A. J., Black, J., and Farsetta, K. The Serological Types of *Shigella Paradysenteriae* (Flexner) II. Types with a Single Primary Antigen, *J. Immunol.* **49**:321-340 (Dec) 1944, II. Types with Dual Primary Antigens. Practice of Typing, Discussion, *ibid.* **49**:341-351 (Dec) 1944.

159 Morton, H. E., and Engley, F. B. Dysentery Bacteriophage, *J. A. M. A.* **127**:584-591 (March 10) 1945.

160 Perlman, E., Binkley, F., and Goebel, W. F. Studies on the Flexner Group of Dysentery Bacilli, *J. Exper. Med.* **81**:349-358 (April) 1945.

161 Watt, J., and DeCapito, T. M. Studies of Acute Diarrheal Diseases. XV. The Agglutination Test in *Shigella Paradysenteriae* Infections, *Pub. Health Rep.* **60**:642-650 (June 8) 1945.

152 Havens, W. P., Paul, J. R., and VanRooyen, C. E. Human Transmission of Infectious Hepatitis by the Oral Route, *Lancet* **1**:202-203 (Feb 17) 1945. Findlay, G. M., and Willcox, P. R. Transmission of Infected Hepatitis by Feces and Urine, *ibid.* **1**:212 (Feb 17) 1945. MacCallum, F. O., and Bradley, W. H. Transmission of Infective Hepatitis to Human Volunteers, *ibid.* **2**:228-229 (Aug 12) 1944.

153 Neefe, J. R., Stokes, J., Reinhold, J. G., and Lukens, F. D. W. Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, *J. Clin. Investigation* **23**:836-855 (Sept) 1944.

154 Stokes, J., and Neefe, J. R. The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin, *J. A. M. A.* **127**:144-145 (Jan 20) 1945.

155 Benjamin, J. E., and Hoyt, R. C. Disability Following Postvaccinal (Yellow Fever) Hepatitis. A Study of Two Hundred Patients Manifesting Delayed Convalescence, *J. A. M. A.* **128**:319-323 (June 2) 1945.

156 Pollock, M. R., and Harris, A. D. Therapeutic Trial of Methionine in Infectious Hepatitis, *Brit. M. J.* **1**:399-401 (March 24) 1945. Higgins, G., O'Brien, J. R. P., Peters, R. A., Stuart, A., and Witts, L. J. Treatment of Infectious Hepatitis with Methionine, *Brit. M. J.* **1**:401-402 (March 24) 1945.

157 Watt, J., and Hardy, A. V. Studies of the Acute Diarrheal Diseases. XIII. Cultural Surveys of Normal Population Groups, *Pub. Health Rep.* **60**:261-273 (March 9) 1945. Hardy, A. V., and Watt, J. XIV. Clinical Observations, *ibid.* **60**:521-531 (May 11) 1945.

*Typhoid*—The use of streptomycin for typhoid has been discussed. According to Luippold, the standard subcutaneous method of vaccination against typhoid is superior to one tenth or one fifth of the dose given intracutaneously.<sup>162</sup> The latter is useful chiefly for elderly persons and for allergic persons, for whom the intracutaneous injection of small doses is safer.

*Cholera*—In a series of papers in the December issue of the *Proceedings of the Society of Experimental Biology and Medicine*, Burrows and his associates report the isolation and properties of the endotoxin of the cholera vibrio. It is resistant to peptic and tryptic digestion and is possibly a phospholipid. Mice could be actively immunized with the toxin, but neutralization in vitro was not accomplished with either antibacterial or antiendotoxic serums known to be protective for mice. Mice could not be immunized against the intraperitoneal injection of endotoxin. Active immunity in human beings probably includes both antitoxic and antibacterial protection. A trial of streptomycin for the treatment of cholera is in order.

*Ulcerative Colitis*—In considering types of ulcerative colitis on an etiologic basis, Bargaen<sup>163</sup> still regards the streptococcus as a cause. With great numbers of streptococci usually present normally in the bowel and its wall and with no proof of their pathogenicity, he still advocates the use of an antistreptococcus vaccine and, what is even more futile, the removal of teeth and tonsils as foci of infection. No mention is made of the importance of psychic influence in the disease.

*"Vincent's Infection"*—According to dentists' views,<sup>164</sup> the etiology and epidemiology of ulcerative gingivostomatitis (Vincent's disease) are poorly understood. It is indeed an important disease, but it is not even known whether it is contagious or not or whether the spiral microorganisms usually associated with the disease are the cause. In one study, improvement of oral hygiene was therapeutically effective. In another, the technic for the isolation and culti-

vation of spirochetes from gingival lesions is described.

It is doubtful that sulfonamide compounds are of specific value in treatment.<sup>165</sup> The efficacy of penicillin therapy of the condition is uncertain, although one report,<sup>166</sup> made without control studies, is favorable. Patients treated with penicillin also received other hygienic oral treatment, which, as previously mentioned, is in itself effective. The use of penicillin was based on the analogy of its success in the treatment of syphilis and other spirochetal diseases, but just the fact that Vincent's spirochete is curly like other spirochetes is not reason enough to support the theory. At one time arsphenamines were used for the same reason, regardless of the fact that patients at times contracted Vincent's infections while undergoing intensive arsphenamine treatment for syphilis. Both penicillin and sulfonamide compounds may, indeed, influence favorably infections caused by gingival bacteria susceptible to their effects, but until further controlled study is made judgment should be reserved.

#### DISEASES OF THE CENTRAL NERVOUS SYSTEM

*Poliomyelitis*—Toomey<sup>167</sup> warns against the use of sulfonamide therapy for poliomyelitis. It may be harmful.

In an epidemiologic study of poliomyelitis, reported by Pearson and his associates in the March number of the *American Journal of Hygiene*, specimens of stools from almost all people in a village where 1 case occurred were studied. Virus was recovered only from a son of the patient. Of 30 other persons associated with a patient, virus was recovered in the stools of only 3. Virus was not found in feces of farm animals or in flies, mosquitoes, rats or mice in the vicinity. It seemed that personal association was the principal factor involved in the spread of the virus. In an outbreak in a city, no evidence of sanitary defects was found, nor was any single source of food or milk incriminated. Mosquitoes, flies, rats and mice were not numerous. Virus was most often found among persons of a household in which a patient was present. Instead of a random scattering of cases, the distribution was concentrated about the

162 Luippold, G. F. Typhoid Vaccine Studies. IX. Intracutaneous Versus Subcutaneous Vaccination for Initial Immunization, *Am J Pub Health* **34** 1151-1162 (Nov.) 1944.

163 Bargaen, J. A. The Medical Management of Ulcerative Colitis, *J A M A* **126** 1009-1013 (Dec 16) 1944.

164 Dunn, H. T., and Singleton, D. E. Vincent's Infection—A Wartime Disease, *Am J Pub Health* **35** 433-440 (May) 1945. Hamp, E. G. Vincent's Infection—A Wartime Disease, *ibid* **35** 441-450 (May) 1945.

165 Manson, W. W., and Craig, I. T. Treatment of Vincent's Angina with Sulfathiazole, *J A M A* **127** 277 (Feb 3) 1945.

166 Pearce, W. F., and McDonald, J. B. Treatment of Ambulatory Patients with Penicillin Sodium, *J A M A* **128** 342-344 (June 2) 1945.

167 Toomey, J. A. Treatment of Poliomyelitis, *J A M A* **126** 49 (Sept 2) 1944.

source in a patient who served as a focus of infection. Others<sup>168</sup> found poliomyelitis virus in the oropharynx of nearly half of 23 patients but never after the third day of disease. Horstman and her associates<sup>169</sup> show that poliomyelitis virus persists in the feces of patients for variable periods after an attack but not permanently. Sixty-one per cent of patients excreted virus for two weeks after the onset of the disease, but the percentage gradually declined until only 12 per cent did after eight weeks. Only 1 excreted virus in the twelfth week.

From another study<sup>170</sup> the first direct evidence of the serving of contaminated food as a link in the chain of infection was derived. Food exposed to flies in homes where patients had the disease contained enough virus to cause mild forms of poliomyelitis in chimpanzees which ate the contaminated food. Poliomyelitis can obviously be transmitted in a number of ways.

In a study of noncontact persons during an interepidemic period,<sup>171</sup> tonsils and stools were collected from 136 persons. At least 5 of these persons harbored poliomyelitis virus, either in their tonsils or in their feces when the disease was not present in the community.

A case of a second attack of poliomyelitis in a woman of 32 is reported.<sup>172</sup> The first occurred thirteen years previously. Howe and Bodian<sup>173</sup> observed the apparent spontaneous infection of 2 chimpanzees with poliomyelitis. Melnick<sup>174</sup> isolated poliomyelitis virus from the blood of 4 of 10 infected monkeys.

While numerous earlier experiments show that mice given diets deficient in thiamine are more resistant to poliomyelitis, tests now show that riboflavin deficiency has a much less striking

effect.<sup>175</sup> Incidentally, riboflavin-deficient mice are much less resistant to infections by organisms of the *Salmonella* group than are normally fed mice.<sup>176</sup> The apparent paradox of the fact that both immunity to viral infections and hypersusceptibility to bacterial diseases can stem from hypovitaminosis lacks explanation. Monkeys, unlike mice, are not more resistant to poliomyelitis when fed a thiamine-deficient diet.<sup>177</sup> Hypovitaminosis, therefore, is not related to increased resistance in all species of animals.

Studies by Schneider and Webster<sup>178</sup> illustrate how deceiving conclusions may be in regard to the effect of nutrition on resistance to infection if the results are not carefully controlled. Certain diets may indeed promote a higher survival rate in experimentally infected mice, but the differences noted depend largely on the genetic constitution of the mice used for study. The results of certain reported studies could not be duplicated in highly inbred strains of mice of known natural resistance.

During an epidemic of poliomyelitis in Iowa in 1943, 10 cases of another unclassified disease were observed,<sup>179</sup> characterized by a sudden onset of high fever, anorexia and nausea, headache, photophobia, backache and pains in the limbs, occurring chiefly in children and young adults and lasting about a week. The only epidemiologic feature of possible significance was a history of swimming in rivers or lakes by over half of the victims. The authors believe that previous similar outbreaks—an outbreak in Georgia in 1940 also associated with swimming and two outbreaks in California in 1934 and 1935—which may or may not have been of the same disease, were described in 1943 as "pretibial fever." The disease observed did not seem likely to be related to Bullis fever or to Colorado tick

168 Howe, H. A., Bodian, D., and Wenner, H. A. Further Observations on the Presence of Poliomyelitis Virus in the Human Oropharynx, *Bull. Johns Hopkins Hosp.* **76**: 19-24 (Jan.) 1945.

169 Horstman, D. M., Ward, R., and Melnick, J. L. Persistence of Virus Excretion in the Stools of Poliomyelitis Patients, *J. A. M. A.* **126**: 161-162 (Dec. 23) 1944.

170 Ward, R., Melnick, J. L., and Horstman, D. M. Poliomyelitis in Fly-Contaminated Food Collected at an Epidemic, *Science* **101**: 491-493 (May 11) 1945.

171 Kessel, J. F., and Moore, F. J. Occurrence of Poliomyelitis Virus in Tonsils and Stools of Non-contacts During an Interepidemic Period, *Am. J. Hyg.* **41**: 25-29 (Jan.) 1945.

172 Wyllie, J. Second Attack of Poliomyelitis After Thirteen Years, *Canad. J. Pub. Health* **36**: 156-159 (April) 1945.

173 Howe, H. A., and Bodian, D. Poliomyelitis by Accidental Contagion in the Chimpanzee, *J. Exper. Med.* **80**: 383-390 (Nov.) 1944.

174 Melnick, J. L. Poliomyelitis Virus in the Blood Stream in the Experimental Disease, *Proc. Soc. Exper. Biol. & Med.* **58**: 14-16 (Jan.) 1945.

175 Rasmussen, A. F., Jr., Waisman, H. A., and Lichstein, H. C. Influence of Riboflavin in Susceptibility of Mice to Experimental Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **57**: 92-95 (Oct.) 1944.

176 Kligler, I. J., Guggenheim, K., and Buechler, E. Relation of Riboflavin Deficiency to Spontaneous Epidemics of *Salmonella* in Mice, *Proc. Soc. Exper. Biol. & Med.* **57**: 132-133 (Oct.) 1944.

177 Clark, P. F., Waisman, H. A., Lichstein, H. C., and Jones, E. S. Influence of Thiamine Deficiency in *Macaca Mulatta* in Susceptibility to Experimental Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **58**: 42-45 (Jan.) 1945.

178 Schneider, H. A., and Webster, L. T. Nutrition of the Host and Natural Resistance to Infection, *J. Exper. Med.* **81**: 359-384 (April) 1945.

179 Paul, W. D., Antes, E. H., and Sahs, A. L. A Dengue-like Fever Occurring in Iowa During the Poliomyelitis Epidemic of 1943, *Arch. Int. Med.* **75**: 184-191 (March) 1945.

fever. The authors prefer to call the disease a "dengue-like" fever. Differentiation from poliomyelitis or meningoencephalitis was made by study of the spinal fluid.

*Encephalitis*—Encephalitis was found at necropsy in 1 patient with herpes simplex<sup>180</sup> and in 1 with herpes zoster<sup>181</sup>. In both instances, the histologic changes were not specific, and the diagnosis could be made only by association with other factors. In the case of herpes zoster, its etiologic relation with encephalitis was not clear. Mumps meningitis is commented on elsewhere in this review.

In an epidemic of pleurodynia<sup>182</sup> affecting 16 nurses, symptoms of involvement of the central nervous system were striking, suggesting that the causative agent was neurotropic, as many as 76 leukocytes per cubic millimeter were found in the spinal fluid. Five of the attacks were preceded by mild infections of the upper respiratory tract, and gastrointestinal symptoms were common, as in the syndrome viral dysentery already mentioned.

Although mosquitoes were known to be able to convey St. Louis encephalitis to chickens experimentally, new evidence<sup>183</sup> also incriminates chicken mites as inter-fowl transmitters. Chicken mites and ticks collected in Texas, where epidemics of equine encephalitis occurred, were found to contain the virus of this disease also<sup>184</sup>. They may be the actual natural reservoirs or vectors of both diseases and perhaps of still others. These discoveries suggest certain clear-cut problems in prophylaxis.

Evidence<sup>185</sup> of the existence of even more unknown viruses appears, three neurotropic viruses different from any known ones were isolated from mosquitoes in South America.

*Tuberculous Meningitis*—Jennings<sup>186</sup> describes 2 of the few reported cases of recovery

from tuberculous meningitis. It seems probable, however, that many more unrecognized nonfatal cases occur which are not diagnosed, either because of the mildness of the symptoms or because the spinal fluid is not studied or tubercle bacilli cannot be found. In other studies, streptomycin had no influence on the course in several cases.

*Tetanus*—Under the title of "A New Method of Treating Tetanus," Stern<sup>187</sup> recommends the cisternal injection of antitetanus serum. There is nothing new about this, in fact, the procedure has long been condemned as futile and dangerous. Apparently Soviet investigators have not had access to the papers of Abel and many other clinical reports in the English language.

*Rheumatic Fever*—If experiments reported by Copeman<sup>188</sup> can be confirmed, current ideas as to the cause of rheumatic fever must be revised. Blood from a patient with rheumatic fever was injected into 5 volunteers, in 2 of whom mild attacks developed. Blood from these 2 was injected into 4 more volunteers and caused the appearance of symptoms in 1. Transmission was successful once again but failed thereafter. The experiment recalls that of Birkhaug, who caused symptoms to appear in himself by inoculating a filtrate of a strain of nonhemolytic streptococci. Also of interest in this connection is a report by MacNeal and his associates<sup>189</sup> on the production of a nonbacterial form of verrucous endocarditis in rabbits by the intravenous injection of filtered pericardial exudate from a patient with rheumatic carditis. Endocarditis was also caused by the injection of exudates and blood from other patients but with inconstant results. The infection could be propagated from rabbit to rabbit and was apparently grown in embryonated eggs. As usual, difficulties were encountered in differentiating the lesions from those found in rabbits subjected to various other experimental procedures.

In a study of 32 cases, according to Copeman,<sup>190</sup> rheumatic fever was found to be an endogenous disease provoked into clinical significance by preceding conditions which may not be streptococcal in origin, such as exposure, cold

180 Hassin, G. B., and Rabens, I. A. Herpetic meningoencephalitis. Clinical-Pathologic Report of Case, *J. Neuropath. & Exper. Neurol.* **3**: 355-367 (Oct) 1944.

181 Krumholz, S., and Luhan, J. A. Encephalitis associated with Herpes Zoster. Report of Case, *Arch. Neurol. & Psychiat.* **53**: 59-67 (Jan) 1945.

182 McConnell, J. An Epidemic of Pleurodynia with Prominent Neurologic Symptoms and No Demonstrable Cause, *Am. J. M. Sc.* **209**: 41-48 (Jan) 1945.

183 Smith, M. G., Blattner, R. J., and Heys, F. M. The Isolation of the St. Louis Encephalitis from Chicken Mites (*Dermanyssus Gallinae* in Nature), *Science* **100**: 362-363 (Oct 20) 1944.

184 Sulkin, S. E. Recovery of Equine Encephalomyelitis Virus (Western Type) from Chicken Mites, *Science* **101**: 381-383 (April 13) 1945.

185 Roca-Garcia, M. The Isolation of Three Neurotropic Viruses from Forest Mosquitoes in Eastern Colombia, *J. Infect. Dis.* **75**: 160-169 (Sept-Oct) 1944.

186 Jennings, G. H. Recovery from Tuberculous Meningitis, *Lancet* **1**: 466-467 (April 14) 1945.

187 Stern, L. A. A New Method of Treating Tetanus, *Am. Rev. Soviet Med.* **1**: 540-543 (Aug) 1944.

188 Copeman, W. S. C. Experimental Transmission of Rheumatic Fever, *Ann. Rheumat. Dis.* **4**: 37-39 (Dec) 1944.

189 MacNeal, W. J., Blevins, A., Slavkin, A. E., and Scanlon, H. Experimental Verrucous Endocarditis, *Science* **101**: 415-416 (April 20) 1945.

190 Copeman, W. S. C. Observations on the Natural History of Acute Rheumatic Fever, *Ann. Rheumat. Dis.* **4**: 11-17 (Sept) 1944.

and fatigue. In only a few instances was there a suggestion of transmission by droplets or by air. He believes rheumatic fever to be basically an acute progressive febrile fibrositic reaction localized in tendon sheaths near joints.

A symposium on rheumatic fever is reported in the October 21 issue of the *Journal of the American Medical Association*. In it Wilson and Lubshez express doubt that the role of hemolytic streptococcal infection in precipitating rheumatic occurrences has been proved by several studies in which sulfonamide prophylaxis supposedly reduced the incidence of the disease. The published data, they state, do not meet the basic requirements for adequate biostatistical analysis. On the other hand, according to Jones, epidemiologic data from military sources seem to indicate close association of rheumatic disease with hemolytic streptococcal infections. He outlines the criteria for reasonably certain diagnosis of the disease. He like Wilson, also refuses to accept as proved the evidence that sulfonamide prophylaxis is reliable in preventing recurrences of the disease and properly regards it still as an experimental measure. Thomas maintains her previous view that sulfonamide prophylaxis is the most effective measure of preventing recurrences. She recommends 1 Gm. of sulfadiazine daily for at least five years. One of her patients has received this dose for eight years. One wonders if the evidence of superiority of penicillin for hemolytic streptococcal infections will cause a change of these views.

Not long ago Coburn recommended massive doses of sodium salicylate to be given intravenously for the treatment of rheumatic fever. Subsequently, deaths and severe complications were reported<sup>191</sup> in patients receiving large doses. Salicylic poisoning was seldom considered in the past, but it is, nevertheless, dangerous.

*Rheumatoid Arthritis*—Freund and his associates<sup>192</sup> report a novel view of the pathology of rheumatoid arthritis. In 14 patients they found inflammatory nodules widely disseminated in the peripheral nerve trunks and muscles. Control studies on nonarthritic patients failed to show these lesions. The changes, they believe, serve to explain the clinical manifestations of the disease and show that it is a systemic one not confined to the joints. One wonders why such striking changes had not been noted or reported by other investigators before, whether in certain

cases they may not be an effect rather than a cause and what then relation is to the well known subcutaneous nodules found in this disease.

#### OTHER VIRAL DISEASES

*Mumps*—With the idea in mind of immunizing children against mumps at an age when the disease is supposedly not dangerous, an epidemic was permitted to spread unchecked in a school<sup>193</sup>. Out of 161 exposed children, 114 were susceptible. Of these, 62 contracted mumps, 4 with encephalitis, 1 with orchitis and 1 with pancreatitis. Besides these, 10 members of the families of these children had mumps. The school physician decided it would be unwise to repeat the experiment. Experimental evidence<sup>194</sup> suggests that in most circumstances mumps, in contrast with chickenpox, is not a true air-borne disease.

In experiments by Enders and his associates,<sup>195</sup> monkeys were infected by the intraparotid injection of saliva from patients. An antigen appeared in the gland which reacts with the serum of convalescent monkeys. In human beings, a specific antibody appears in the serum regularly during and after the disease. Specific dermal hypersensitivity and complement-fixing antibodies in the serum developed in convalescent patients. The complement fixation test is especially valuable in the difficult diagnosis of mumps encephalitis when parotitis is minimal, delayed or absent. The reaction was positive in 16 of 50 patients with encephalitis without involvement of the parotid gland. It would probably be valuable also in the diagnosis of mumps pancreatitis or orchitis.

Mumps virus in large amounts for use in the complement fixation test can be obtained from chick embryo cultures<sup>196</sup>. Egg virus facilitates the possible development of vaccine, material for cutaneous tests and other aids in the study of mumps.

193 Levine, M. I. Sponsored Epidemic of Mumps in a Private School, *Am J Pub Health* **34** 1274-1276 (Dec.) 1944.

194 Habel, K. Mumps and Chickenpox as Air-Borne Diseases, *Am J M Sc* **209** 75-78 (Jan.) 1945.

195 Enders, J. F., Kane, L. W., Cohen, S., and Levens, J. H. Immunity in Mumps. I. Experiments with Monkeys (*Macacus Mulatta*), *J Exper Med* **81** 93-118 (Jan.) 1945. Enders, J. F., Cohen, S., and Kane, L. W. II. Development of Complement-Fixing Antibody and Dermal Hypersensitivity in Human Beings Following Mumps, *ibid* **81** 119-136 (Jan.) 1945. Kane, L. W., and Enders, J. F. III. Complement Fixation Test as Aid in Diagnosis of Mumps Meningo-encephalitis, *ibid* **81** 137-150 (Jan.) 1945.

196 Habel, K. Cultivation of Mumps Virus in the Developing Chick Embryo and Its Application to Studies of Immunity to Mumps in Man, *Pub Health Rep* **60** 201-217 (Feb. 23) 1945.

191 Ashworth, C. T., and McKernie, J. F. Hemorrhagic Complications with Death Probably from Salicylate Therapy, *J A M A* **126** 806-810 (Nov. 25) 1944.

192 Freund, H. A., Steiner, G., Leichtentritt, B., and Price, A. E. Nodular Polymyositis in Rheumatoid Arthritis, *Science* **101** 202-203 (Feb. 23) 1945.

That mumps should be considered a general systemic infection is pointed out by Swedish clinicians<sup>197</sup> The parotid glands are usually involved but not always Among 458 patients in an epidemic, changes in the spinal fluid indicated meningeal involvement in 65 per cent In 10 per cent, meningeal involvement preceded swelling of the parotid gland In support of the view of Enders just mentioned, mumps is suggested as a cause of certain undiagnosed attacks of lymphocytic meningitis From electrocardiographic evidence Rosenberg<sup>198</sup> concludes that, contrary to general belief, the myocardium is often involved during mumps Of 104 patients, transient electrocardiographic changes appeared in 16

*Measles*—Gamma globulin is better than placental globulin for the prophylaxis of measles<sup>199</sup> Among 814 children exposed to the disease and treated, none had regular measles, 78 per cent were completely protected, and the rest had mild attacks Concentrated gamma globulin, when given in the first six days after exposure to the disease, will protect 3 out of every 4 persons if it is given in doses of 0.08 to 0.1 cc per pound (0.5 Kg) of body weight<sup>200</sup>

*Smallpox*—Stevenson<sup>201</sup> points out that vaccination against smallpox usually gives reliable protection but in numerous instances it fails There is no justification for the opinion that vaccination within a few days after exposure to smallpox will invariably give immunity to it Unexplained variations in immunity response to vaccine occur in different persons Variations of potency or in the immunizing power of the vaccine cannot always be blamed for failures

In an outbreak among a supposedly highly immunized group,<sup>202</sup> 96 per cent had been vaccinated at some time, 70 per cent within two years and 16 per cent within two months Great variations also occur in the clinical manifestations of the disease itself Accurate clinical

diagnosis in the early stages is often impossible, and little reliance should be placed on details of the typical textbook descriptions, including the three to four day fever, backache and the supposed characteristic eruption The eruption may mimic those of measles or chickenpox Diagnosis was greatly aided by a new test<sup>203</sup> consisting of making scrapings of a papule, staining them on a specially prepared slide and examining them for elementary bodies These bodies are much more numerous than those in the lesions of chickenpox The results of the test were positive in 77 out of 80 cases It is rapid and easily eliminates probable diagnoses of chickenpox, measles or typhus The Paul rabbit eye test is less reliable and takes three days to do

*Psittacosis*—Evidence is presented<sup>204</sup> that epizootics among pigeons may be caused by two viruses simultaneously, one a psittacosis-like virus (ornithosis) and the other a new one called INI (intranuclear inclusion) virus The latter is pathogenic for pigeons but not for rabbits, guinea pigs or mice

Of 113 mixed Amazon parrots and parakeets impounded by quarantine regulations in Brownsville, Texas, 108 died (97 per cent) from psittacosis and bacterial infections, especially those with the *Salmonella* group of bacilli<sup>205</sup>

*Yellow Fever*—For the first time<sup>206</sup> yellow fever was discovered in a wild animal in its natural habitat in South America A sick monkey was trapped and died from the disease The discovery favors the view that the reservoir of jungle yellow fever is in animals, from which it is spread to human beings Antibodies, but no virus, were found in the blood of the other monkeys and in opossums, suggesting past infections with yellow fever virus

*Other Studies on Viruses*—Distemper virus, like the other filtrable viruses, may be modified by passage in hosts other than the usual ones<sup>207</sup> By passing through ferrets, the virulence of canine distemper virus for foxes or dogs declined, and

197 Bang, H O, and Bang, J Involvement of the Central Nervous System in Mumps, *Acta med Scandinav* **113** 487-505 (April) 1943

198 Rosenberg, D H Electrocardiographic Changes in Epidemic Parotitis (Mumps), *Proc Soc Exper Biol & Med* **58** 9-11 (Jan) 1945

199 Greenberg, M, Frant, S, and Rutstein, D D "Gamma Globulin" and "Placental Globulin," *J A M A* **126** 944-947 (Dec 9) 1945

200 Janeway, C A The Use of Concentrated Human Serum  $\gamma$ -Globulin in Prevention and Attenuation of Measles, *Bull New York Acad Med* **21** 202-222 (April) 1945

201 Stevenson, W D H Vaccination Against Smallpox Apparent Anomalies in Protection, *Lancet* **2** 697-700 (Nov 25) 1944

202 Illingworth, R S, and Oliver, W A Smallpox in the Middle East Lessons from One Hundred Cases, *Lancet* **2** 681-685 (Nov 25) 1944

203 van Rooyen, C E, and Illingworth, R S Laboratory Test for Diagnosis of Smallpox, *Brit M J* **2** 526-529 (Oct 21) 1944

204 Smadel, J E, Jackson, E B, and Harman, J W A New Virus Disease of Pigeons I Recovery of the Virus, *J Exper Med* **81** 385-397 (April) 1945

205 Dunnahoo, G L, and Hampton, B C Psittacosis Occurrence in the United States and Report of 97 per cent Mortality in a Shipment of Psittacine Birds While Under Quarantine, *Pub Health Rep* **60** 354-357 (March 30) 1945

206 Fosdick, R B The Rockefeller Foundation A Review for 1944, p 36

207 Green, R G Zoologic and Histologic Modification of the Distemper Virus by Ferret Passage, *Am J Hyg* **41** 7-24 (Jan) 1945

after fifty passages the virus caused only symptomless infection, after further passage, no infection resulted

Habel<sup>208</sup> obtained better results in the protection of animals against rabies by using a concentrated rabies-immune rabbit serum with the usual vaccine method of prophylaxis. Serum prophylaxis combined with vaccine prophylaxis gave even better results. Trial in human beings is warranted.

According to Kramer and his co-workers,<sup>209</sup> who tested the therapeutic and prophylactic action of a wide variety of chemical compounds on neurotropic virus infections in mice, none of the agents had any value. Some effect of sulfonamide compounds and penicillin has been reported on infections of the psittacosis group, but there is still a question as to whether the causative agents are true filtrable viruses.

With an ingenious technique,<sup>210</sup> electron microscopy can now show three dimensional views of virus particles to give new information about their size and shape. In Beard's studies,<sup>211</sup> electron micrographs showed unmistakable evidence of differentiation within virus particles, causing him to favor the idea that viruses are not mere aggregates of molecules but resemble relatively more highly organized bacteria in their shape and internal makeup.

**Tularemia**—In a study<sup>212</sup> in which *Bacterium tularensis* was found to be extremely polymorphous. Foshay and Hesselbrock found some forms to be so minute as to resemble certain elementary bodies. In filtration tests with graded membranes, these minute pathogenic forms passed through and developed into larger units after their inoculation in animals.

A long list of naturally infected vertebrates was published.<sup>213</sup>

In a clinical report<sup>214</sup> on studies made without proper controls, 61 patients with tularemia are said to have been promptly cured by the intravenous injection of a solution of bismuth sodium tartrate. The details of the investigation are so meager as to render further judgment of the report impossible. In experimental studies<sup>215</sup> on guinea pigs a variety of medicaments, including sulfonamide compounds, penicillin, iodide and bismuth compounds, an arsenical, an antimony compound and antitularemic serum, were found to be of no value in treatment. It is possible that streptomycin will prove to be the most effective therapeutic agent.

Many more persons are bitten by rats than is usually thought.<sup>216</sup> In a study of an area of 2 square miles (approximately 5 square kilometers) in Baltimore, it was learned that a minimum of 93 persons were bitten in a four year period and in 7 (14 per cent) rat bite fever developed.

**Rickettsial Diseases**—Attention is called to the dangers of circulatory collapse associated with typhus<sup>217</sup> and with Rocky Mountain spotted fever<sup>218</sup> and to the need for appropriate supportive therapy. A great deal of nonsense has also been advocated. In one instance,<sup>219</sup> sulfonamide compounds were given "as a matter of routine" before diagnosis was made, then penicillin was given, and the fever fell. In another,<sup>218</sup> quinine sulfate was given, despite the current shortage, then, among other things, metaphen intravenously for ten days, then calcium chloride and vitamins intravenously, then sulfadiazine and finally roentgenotherapy. The patient recovered anyway.

A report<sup>220</sup> on the use of antityphus serum is not impressive. Serum apparently had a bene-

214 Jackson, W. W. The Treatment of Tularemia with Intravenous Bismuth Sodium Tartrate, *Am J M Sc* **209** 513-520 (April) 1945

215 Bell, J. F., and Kalm, O. B. Efficacy of Some Drugs and Biologic Preparations as Therapeutic Agents for Tularemia, *Arch Int Med* **75** 155-158 (March) 1945

216 Richter, C. P. Incidence of Rat Bites and Rat Bite Fever in Baltimore, *J A M A* **128** 324-326 (June 2) 1945

217 Woodward, T. E., and Bland, E. F. Clinical Observations in Typhus Fever with Special Reference to the Cardiovascular System, *J A M A* **126** 287-290 (Sept 30) 1944

218 Harrell, G. T., Venning, W., and Wolff, W. A. The Treatment of Rocky Mountain Spotted Fever, *J A M A* **126** 929-934 (Dec 9) 1944

219 Edmunds, P. K. Rocky Mountain Spotted Fever Treatment with Penicillin, *Rocky Mountain M J* **41** 910-912 (Dec) 1944

220 Stevens, R. S. Louse-Borne Typhus Fever Trial of Serum Treatment, *Lancet* **1** 106-109 (Jan 27) 1945

208 Habel, K. Seroprophylaxis in Experimental Rabies, *Pub Health Rep* **60** 545-560 (May 18) 1945

209 Kramer, S. D., Gier, H. A., and Szobel, D. A. The Chemoprophylactic and Therapeutic Action of a Wide Variety of Chemical Compounds on True Neurotropic Virus Infections in Mice, *J Immunol* **49** 273-314 (Nov) 1944

210 Williams, R. C., and Wyckoff, R. W. G. Electron Shadow-Micrographs of Virus Particles, *Proc Soc Exper Biol & Med* **58** 265-270 (March) 1945

211 Beard, J. W. The Ultracentrifugal, Chemical and Electron Micrographic Characters of Purified Animal Viruses, *Proc Inst Med Chicago* **15** 294, 1945

212 Foshay, L., and Hesselbrock, W. Some Observations on the Filtrability of *Bacterium Tularensis*, *J Bact* **49** 233-236 (March) 1945

213 Burroughs, A. L., Holdenried, R., Longanecker, D. S., and Meyer, K. F. A Field Study of Latent Tularemia in Rodents with a List of All Known Naturally Infected Vertebrates, *J Infect Dis* **76** 115-119 (March-April) 1945

ficial effect in modifying the severity of the disease in a few patients

#### EXOTIC DISEASES

Sapero and Butler<sup>221</sup> review the infectious diseases which caused our naval forces the most concern in the South Pacific area namely, malaria, bacillary dysentery, dengue, filariasis, infectious hepatitis and tsutsugamushi fever (scrub typhus). They point out how effectively malaria can be controlled even under combat conditions, chiefly by the control and elimination of the breeding areas of anopheles mosquitoes, by the proper use of chemical repellents and insecticides, by screening and by medication. One of the greatest factors in the prevention of malaria, dengue and filariasis was the separation or isolation of our personnel from infected natives who served as sources of infection. Dengue is also preventable by effective measures to prevent the breeding of mosquitoes and their access to patients with the disease. Bacillary dysentery was effectively controlled by reducing the number of flies by proper disposal of garbage and fecal matter and by the use of screens.

**Malaria**—In a study<sup>222</sup> of soldiers returning to this country with malaria contracted in the South Pacific area, the acute recurrent attacks, mostly of *Plasmodium vivax* origin, were found to be relatively mild. Quinacrine hydrochloride was effective in ridding the blood of parasites and in controlling symptoms. The rate of recurrences diminished with the passage of time. In spite of the good immediate results of therapy with quinacrine hydrochloride, the large number of relapses is a problem. Many patients also complain of not feeling well between attacks. Symptoms suspected as psychoneurotic in origin were often encountered.

The apparent transmission of malaria from a soldier returned from the Pacific area to 2 persons is reported<sup>223</sup> from an area in Oregon previously free from the disease. Mosquitoes were abundant at the time (*Anopheles punctipennis* and *maculipennis*).

Sulfadiazine is of no value in preventing relapses of malaria caused by a strain of *P. vivax*.

221 Sapero, J J, and Butler, F A. Highlights on Epidemic Diseases Occurring in Military Forces in the Early Phases of the War in the South Pacific, *J A M A* **127** 502-506 (March 3) 1945.

222 Gordon, H H, and others. Clinical Features of Relapsing *Plasmodium Vivax* Malaria in Soldiers Evacuated from the South Pacific Area, *Arch Int Med* **75** 159-167 (March) 1945.

223 Osgood, S B. Malaria and the Returning Soldier, *J A M A* **128** 512-513 (June 16) 1945.

malaria in the Southwest Pacific area<sup>224</sup>. The drug should not be used. The rate of relapse of this form of malaria is high and is not controlled by quinine, quinacrine hydrochloride (atabrine) or pamaquine naphthoate (plasmo-chin). It is also not generally known that there are striking clinical differences among infections caused by different strains of the same type and between naturally acquired and induced malaria, induced malaria is easily controlled with quinine, and there are no relapses.

*Plasmodium malariae* is inactivated by exposure to roentgen rays and is most sensitive during the process of division<sup>225</sup>.

Report<sup>226</sup> is made of the first successful cultivation of *P. knowlesi* in culture medium.

**Dengue**—By passage of the virus of dengue through mice it becomes modified to such an extent that it may serve as an effective vaccine<sup>227</sup>.

**Filariasis**—Extensive studies are being made on filariasis. In the Pacific area, military personnel have shown evidence of infections clinically<sup>228</sup> and histologically<sup>229</sup> three months after arrival. The usual history is of painful intermittent swelling of the testicle for weeks or months. Diagnosis is made by biopsy, by the finding of microfilarias in the blood and by observation of calcified worms by roentgenography. Derivatives of antimony, including lithium antimony thiomalate, are giving encouraging results in treatment<sup>230</sup>.

224 Coggeshall, L T, Martin, W B, and Bates, R D. Sulfadiazine in Treatment of Relapsing Malarial Infections Due to *Plasmodium Vivax*, *J A M A* **128** 7-8 (May 5) 1945.

225 Bennison, B E, and Coatnev, G R. Inactivation of Malarial Parasites by X-Rays, *Pub Health Rep* **60** 127-129 (Feb 2) 1945.

226 Ball, E G, and others. In Vitro Growth and Multiplication of the Malaria Parasite, *Plasmodium Knowlesi*, *Science* **101** 542-544 (May 25) 1945.

227 Sabin, A B, and Schlesinger, R W. Production of Immunity to Dengue with Virus Modified by Propagation in Mice, *Science* **101** 640-642 (Jan 22) 1945.

228 King, B G. Early Filariasis. Diagnosis and Clinical Findings, *Am J Trop Med* **24** 285-298 (Sept) 1944. Byrd, E E, St Arnant, L S, and Bromberg, L. Studies on Filariasis in the Samoan Area, *U S Nav M Bull* **44** 1-20 (Jan) 1945.

229 Wartman, W B. Lesions of Lymphatic System in Early Filariasis, *Am J Trop Med* **24** 281-284 (Sept) 1944. Clinicopathologic Study of Early Filariasis with Lymph Node Biopsies, *U S Nav M Bull* **44** 27-36 (Jan) 1945.

230 Research on Filariasis, *Foreign Letters*, *J A M A* **127** 475 (Feb 24) 1945.

Among 5,000 persons examined<sup>214</sup> for filariasis in Belém Brazil 11 per cent harbored microfilarias (*Wuchereria bancrofti*). The principal vector is the mosquito *Culex fatigans*, 12 per cent of which were found on examination to carry the parasite.

A case of American leishmaniasis caused by *Leishmania braziliensis* apparently originating in the United States was reported.<sup>22</sup> The disease is probably much more common in this country than is realized though probably unrecognized.

*Schistosomiasis*.—Although, as reported by Koppisch several years ago, no snails in this country are known to serve as natural hosts to the causative agent of schistosomiasis, *Schistosoma mansoni*, evidence now shows<sup>23</sup> that potential carriers do exist. A native snail *Iropicorbis havanensis*, was experimentally infected with *S. mansoni*. The acquisition of a natural infection is theoretically possible if these snails become exposed to the excreta of returned military personnel suffering from the disease.

An important point is raised by Bercovitz and his associates,<sup>24</sup> who show that in schistosomiasis, as in other diseases, so-called carriers may actually have the disease and that the actual incidence of the disease, including all mild forms, is much greater than is usually believed. By proctoscopic examination actual ulcerations were found in 60 per cent of 155 otherwise healthy Puerto Ricans who shed ova of *S. mansoni* in their feces. According to the authors, healthy carriers of the disease are to be regarded as infected persons.

*Granuloma Inguinale*.—The causative agent of granuloma inguinale has been cultivated in chick embryos.<sup>25</sup> A new name, *Donovania*

granulomatis, is proposed for the micro-organism, which is probably a bacterium. Washed suspensions of the agent when injected intradermally elicit a strong reaction in twenty-four hours in the active stage of the disease. A mucoid substance, probably capsular in origin, when mixed with serum caused precipitation and complement fixation. These reactions may be of diagnostic value.

*Pinta*.—After previous reported attempts had failed, two Cubans<sup>26</sup> successfully transmitted pinta to rabbits by inoculating them with *Trepionema carateum* obtained from a patient. A papule developed one hundred and five days later at the point of inoculation in 1 of 4 rabbits. A volunteer contracted the disease when inoculated with material from the rabbit.

*Leprosy*.—By using a special stain, non-acid-fast, "zooglyphic" forms or phases of both *Mycobacterium tuberculosis* and *Mycobacterium leprae* can be shown.<sup>27</sup> The existence of the organisms in such forms may account for the difficulty in finding them in certain instances unless the special staining technic is used.

A new disease in horses and man, stachybotryotoxicosis, is described by Diobotko.<sup>28</sup> In horses there are necrotic ulcers in the mouth and throat, hemorrhage, lymphadenopathy and leukopenia reminiscent of glanders, yet the disease does not seem to be contagious and is apparently contracted by the consumption of hay containing the mold *Stachybotrys alternans*. The fact that healthy horses fed moldy hay and feed mixed with cultures of the mold always become infected suggests the etiologic relation. Persons are occasionally infected by contact with the infected hay and have erythema, pharyngitis and rhinitis with bloody exudate, cough and leukopenia without fever. The author goes far afield when he suggests that this mold may be the cause of acute agranulocytosis.

#### ANTIBODY FORMATION

After lying dormant for several years,<sup>29</sup> the subject of the site of formation of antibodies has been revived, with special emphasis on the role

231 Causey, O. R., Deane, M. P., DaCosta, O., and Deane, L. M. Studies on the Incidence and Transmission of Filaria, *Wuchereria Bancrofti*, in Belém, Brazil, *Am J Hyg* **41** 143-149 (March) 1945.

232 Stewart, C. D., and Pilcher, J. F. American Leishmaniasis. Report of an Autochthonous Case, *Arch Dermat & Syph* **51** 124-128 (Feb) 1945.

233 Cram, E. R., Jones, M. F., and Wright, W. A Potential Intermediate Host of *Schistosoma Mansoni*, *Science* **101** 302 (March 23) 1945.

234 Bercovitz, Z. T., Rodriguez-Molina, R., Hargrave, D. W., Dickie, J. D., and Green, C. E. Studies on Human *Schistosoma Mansoni* Infections. I. Proctoscopic Picture in Asymptomatic *Schistosomiasis Mansoni* Infections, *J A M A* **125** 961-963 (Aug 5) 1944.

235 Anderson, K., DeMonbreun, W. A. and Goodpasture, E. W. An Etiologic Consideration of *Donovania Granulomatosis* Cultured from *Granuloma Inguinale* (Three Cases) in Embryonic Yolk, *J Exptl Med* **81** 25-39 (Jan) 1945. Anderson, K., Goodpasture, E. W., and DeMonbreun, W. A. Immunologic Relationship of *Donovan* Granulomatosis to *Granuloma Inguinale*, *ibid* **81** 41-50 (Jan) 1945.

236 León-Blanco, F., and Oteiza, A. The Experimental Transmission of Pinta, Mal del Pinto or Curate to the Rabbit, *Science* **101** 309-311 (March 23) 1945.

237 Alexander-Jackson, E. Non-Acid-Fast Forms of the *Mycobacterium* of Human Leprosy, *Science* **101** 563-564 (June 1) 1945.

238 Drobotko, V. G. Stachybotryotoxicosis. A New Disease of Horses and Humans, *Am Rev Soviet Med* **2** 238-242 (Feb) 1945.

239 Reimann, H. A., Medes, G., and Fisher, L. The Origin of Blood Proteins, *Folia haemat* **52** 187-202 1934.

of lymphocytes. In one study,<sup>240</sup> lymphocytes were said to contain a protein probably identical with gamma globulin and were thought to be the site of origin of immune globulin, but the authors make no reference to previous studies on this point or to any others along similar lines. In another recent report,<sup>241</sup> a somewhat broader and perhaps better view is given—namely, that lymphocytes either produce or adsorb antibodies, and other circulating and fixed leukocytic cells also participate in antibody formation. According to another view,<sup>242</sup> lymphocytes do not adsorb antibodies but probably are the site of a change of gamma globulin into an immune substance. Most of these views were held for many years and were embodied in a monograph<sup>243</sup> published in 1941.

Other experiments<sup>244</sup> indicate a control of the number of lymphocytes in the blood and perhaps in other places in the body by secretions of the adrenal cortex. If lymphocytic tissue is as intimately connected with immune responses of the body as is believed by the authors cited in the preceding paragraph, these observations will focus much attention on the role of the anterior pituitary and adrenal glands in the hormonal control of immunity, especially of immunity to infectious diseases accompanied with either lymphopenia or lymphocytosis.

240 Dougherty, T F, Chase, J H, and White, A. The Demonstration of Antibodies in Lymphocytes, *Proc Soc Exper Biol & Med* **57** 295-298 (Nov) 1944

241 Ehrich, W E, and Harris, T N. The Site of Antibody Formation, *Science* **101** 28-31 (Jan 12) 1945  
Harris, T N, and Ehrich, W E. The Role of the Lymphocyte in Antibody Formation, *J Exper Med* **81** 73-83 (Jan) 1945

242 Kass, E H. The Occurrence of Normal Serum Gamma-Globulin in Human Lymphocytes, *Science* **101** 337-338 (March 30) 1945

243 Burnett, F F, Freeman, M, Jackson, A V, and Bush, D. The Production of Antibodies, Melbourne, Australia, Macmillan & Co, Ltd, 1941

244 Reinhardt, W O, and Li, C H. Depression of Lymphocyte Contact of Thoracic Lymph by Adrenocorticotrophic Hormone, *Science* **101** 360-361 (April 6) 1940

According to Cannon<sup>245</sup> there is little hope that optimal nutrition will activate bacteriostatic agents in the defense against infection but inanition may induce a decrease of resistance by interfering with the synthesis of serum globulins, which are important in antibody formation. Globulins seem to play a role in the nonspecific defense against infection.<sup>246</sup> Evidence points more and more to the view that certain aspects of resistance to infection are nutritional or hormonal, but many factors are still unknown.

In dietary studies<sup>247</sup> like those commented on in the paragraphs on poliomyelitis, rats fed a diet deficient in certain vitamins, except thiamine, were more resistant to pneumococcal infections than well fed rats. Inanition itself had no apparent effect on their resistance. Genetic factors must also be considered in interpreting the results of experimental studies.<sup>178</sup>

245 Cannon, P R. Proteins in Resistance to Infection, *J A M A* **128** 360-362 (June 2) 1945

246 Reimann, H A. The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection, *Ann Int Med* **6** 362-374 (Sept) 1932

247 Robinson, H J, and Siegel, H. The Influence of B Vitamin on the Resistance of Rats to Induced Pneumococcal Lobar Pneumonia, *J Infect Dis* **75** 127-133 (Sept-Oct) 1944

## CORRECTION

In the article by Major Robert M Finks and Captain Richard W Blumberg entitled "Epidemic Hepatitis With and Without Jaundice. Some Clinical Studies on Two Hundred and Fifty-Five Patients Among Troops in a Combat Zone" in the August issue (*ARCH INT MED* **76** 102, 1945), sixteen lines from the bottom of the first column on page 110 174 mg of bilirubin should read 174 mg. In the second column of the same page, fifth line of the second paragraph under "Pathologic Data," the word "red" should be "green."

In their proof, which was returned after publication of the article, the authors added the following statement to the fourth new paragraph in the second column on page 111:

"The various tests of hepatic function, such as hippuric acid synthesis and sulfobromophthalein excretion, although used in only a few cases, seemed to be of definite value in diagnosis of this syndrome."

## ESOPHAGEAL LESIONS ASSOCIATED WITH ACROSCLEROSIS AND SCLERODERMA

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The dermatosclerioses constitute a group of diseases in which changes of the connective tissues of the body are predominant. One of us (O'Leary<sup>1</sup>) has discussed four dermatologic entities—namely, scleroderma, acrosclerosis, scleredema and dermatomyositis, all of which have a certain degree of cutaneous sclerosis as part of the clinical picture. Fundamental disturbances of the connective tissues are involved in each of these syndromes. Scleroderma and acrosclerosis are alike in that sclerosing processes take place in the lower portion of the cutis. Acrosclerosis differs from scleroderma in that the trophic disorder in the former appears to have its origin in vasomotor disturbances. Acrosclerosis is a sclerodermic process which involves the distal parts of the extremities and the face and neck of patients who present the phenomena of Raynaud's disease. We believe that it constitutes a distinct clinical entity.

As Weiss and his associates<sup>2</sup> have pointed out, the changes of connective tissue in scleroderma are not confined to the integument. Disturbances of the heart, lungs and gastrointestinal tract have been described in association with scleroderma and allied conditions. Difficulties of deglutition frequently constitute a striking feature of the clinical picture. The oral lesions of scleroderma are well recognized, and the ingestion of food is often difficult because of them. Disturbances of the passage of food through the esophagus are recognized less frequently. It is our purpose to discuss the lesions of the esophagus that may accompany acrosclerosis and scleroderma. Cases of scleredema and dermatomyositis have been excluded from this study.

gus that may accompany acrosclerosis and scleroderma. Cases of scleredema and dermatomyositis have been excluded from this study.

### REVIEW OF THE LITERATURE

In 1903 Ehrmann<sup>3</sup> first recorded the occurrence of dysphagia in a case of acute scleroderma. He performed an esophagosopic examination on the patient and noted changes of the esophageal wall. Since then 31 additional cases have been reported in some detail.<sup>4</sup> All available reports of cases have been studied. The essential facts derived from this review have been summarized in table 1.

TABLE 1—Summary of Data on Cases Reported in the Literature

Total cases reported of scleroderma with esophageal lesions, 32		
Sex: male 7, female 25		
Dermatologic classification (when possible)		27
Acrosclerosis	21	
Scleroderma (generalized)	4	
Acute edematous scleroderma	1	
Localized scleroderma	1	
Roentgenologic features		24
Stenosis in lower part of esophagus	8	
Retardation, lack of motility	11	
Dilatation or cardiospasm	5	
Esophagoscopic features		8
Stenosis in lower part of esophagus	5	
Changes restricted to esophageal wall	3	
Cases in which necropsy was performed		8

The authors of previous articles on this subject were in general agreement that the esophageal disturbances associated with scleroderma are the result of the presence of sclerodermatous changes in the walls of the esophagus. The results of

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1 O'Leary, P. A. *Dermatosclerosis*, *Canad M A J* **48** 410-415 (May) 1943.

2 Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T. *Scleroderma Heart Disease, with Consideration of Certain Other Visceral Manifestations of Scleroderma*, *Arch Int Med* **71** 749-776 (June) 1943.

3 Ehrmann, S. *Ueber die Beziehung der Sklerodermie zu den autotoxischen Erythemen*, *Wien med Wchnschr* **53** 1097-1156, 1903.

4 The four cases reported by Barasciutti (Barasciutti, A. *La disfagia degli sclerodermici, indagini radiologiche e cliniche, rilievi patogenetici e terapeutici*, *Gior di clin med* **18** 885-899 [Oct. 10] 1937) are not included, as the detailed report of cases has not been available for study.

examination at necropsy were described in 8 cases. Grossly, the esophagus usually was dilated, and the mucosa was thickened and had a varnished appearance. In the case reported by Rake<sup>5</sup> there was associated ulcerative esophagitis. In 1 of the cases of Weissenbach, Stewart and Hoesh<sup>6</sup> there was apparent leukoplakia in the lower part of the esophagus. In all the 8 cases, the microscopic observations were similar. The submucosa was thickened and infiltrated with round cells. Fragmentation of elastic fibers was demonstrated, and the muscular layer was atrophied. Perivascular infiltration was also characteristic. In other words, the histologic features were those of sclerosis of the connective tissues.

Roentgenographic studies of the esophagus were carried out in 24 of the cases reviewed in the literature. In 1916 Schmidt<sup>7</sup> made a roentgenoscopic examination of a patient suffering from scleroderma and dysphagia and observed the passage of barium sulfate. Although no lesion was detected in the esophagus, he found that fifteen minutes was required for passage of the barium into the stomach. Kure and his associates<sup>8</sup> made rather elaborate roentgenologic studies of the esophagus in 5 cases of scleroderma. Three of the patients apparently did not have any difficulty in swallowing. Employing a modified barium meal, Kuré and his associates<sup>9</sup> recorded the time required for the passage of the meal from the mouth to the stomach, with the patient both in the upright position and in the dorsal decubitus position. After having established the time intervals for normal subjects, they found that the passage of the meal was retarded greatly for their patients suffering from scleroderma. The retardation was

especially prolonged in the dorsal decubitus position. As might be expected, the greatest delay in passage was noted at the cardia. Weissenbach and his associates<sup>10</sup> made similar time studies in a case of dysphagia, using the technic of Kure and his associates<sup>9</sup>. In addition to the retardation of the bolus, they observed that the normal peristaltic movements were absent and that there were a gaping of the esophagus and a tendency for the barium meal to adhere to the walls of the esophagus. Lindsay and his associates<sup>11</sup> noted reduced peristalsis in 1 of their patients and absence of peristalsis in another.

Dilatation of the esophagus was described by roentgenographic means in the cases of Rake,<sup>5</sup> Nomland<sup>12</sup> and Jackman.<sup>13</sup> The passage of barium was retarded at the cardia in each of these cases. In Jackman's case the barium was retained above the cardia for eight hours. The clinical diagnosis was cardiospasm in each instance.

Stenosis of the lower part of the esophagus has been described in 8 cases by roentgenoscopic study. In 5 of these cases the roentgenologic findings were confirmed by esophagoscopy examination. In Dowling's<sup>14</sup> case the finding of a stricture in the middle segment of the esophagus was not confirmed when necropsy was performed. Fessler and Pohl<sup>15</sup> reported the first stenosing lesion in the lower part of the esophagus in 1932. Lindsay, Templeton and Rothman<sup>11</sup> reported 3 cases in which an obstructing lesion was noted in the lower part of the esophagus. One of their patients (their case 3) is included in our series (case 4), because the patient previously had been a patient

5 Rake, G. On the Pathology and Pathogenesis of Scleroderma, *Bull Johns Hopkins Hosp* **48** 212-227 (April) 1931

6 Weissenbach, R. J., Stewart, W. M., and Hoesh, H. Troubles fonctionnels et lésions de l'oesophage dans la sclérodémie, *Ann de dermat et syph* **79** 81-99 (Feb.), 198-219 (March) 1938

7 Schmidt, R. Sklerodermie mit Dysphagie, *Deutsche med Wchnschr* **2** 1023, 1916

8 (a) Kure, K., Yamagata, K., Tsukada, S., and Hiyoshi, J. Passagestörung des Oesophagus bei Sklerodermie und Dystrophia musculorum progressiva, *Klin Wchnschr* **15** 516-529 (April 11) 1936. (b) Tsukada, S. Röntgenologische Studien über die Veränderungen der Speiseröhre bei progressiver Muskeldystrophie und Sklerodermie, *Mitt d med Gesellsch zu Tokyo* **47** 1914 (Oct) 1933

9 (a) Hiyoshi, J. Beiträge zur Kenntnis der funktionellen Veränderung des Oesophagus durch röntgenologische Untersuchungen bei progressiver Muskeldystrophie und bei Sklerodermie, *Mitt d med Gesellsch zu Tokyo* **51** 799-800 (Aug) 1937. (b) Footnote 8

10 Weissenbach, R. J., Dechaume, Martineau Stewart, W. M., and Hoesh, H. Un cas de syndrome de Thibierge-Weissenbach (sclérodémie progressive et calcifications) avec lésions bucco-pharyngées et oesophagiennes accentuées ayant nécessité la gastrostomie, *Bull Soc franç de dermat et syph* **44** 1053-1060 (June 10) 1937. Weissenbach, R. J., Martineau, Bouwens, Pizon, and di Matteo. Sclérodémie progressive, syndrome de Thibierge-Weissenbach, ulcère de jambe et calcification en mollietiers, troubles oesophagiens, *ibid* **44** 2018-2024 (Dec) 1937

11 Lindsay, J. R., Templeton, F. E., and Rothman, S. Lesions of the Esophagus in Generalized Progressive Scleroderma, *J A M A* **123** 745-750 (Nov 20) 1943

12 Nomland, R. Sclerodactylia with Calcification, *Arch Dermat & Syph* **21** 322-323 (Feb) 1930

13 Jackman, J. Roentgen Features of Scleroderma and Acrosclerosis, *Radiology* **40** 163-168 (Feb) 1943

14 Dowling, G. B. Generalized Scleroderma, *Brit J Dermat* **52** 242-256 (Aug-Sept) 1940

15 Fessler, A., and Pohl, R. Stenosierender Prozess des Oesophagus bei Sklerodermie, *Dermat Ztschr* **63** 164-169 (Feb) 1932

at the Mayo Clinic Weiss and his associates<sup>2</sup> reported 2 cases of scleroderma in which there was organic stenosis in the lower part of the esophagus. In 1 of these cases esophagoscopy examination was performed. They also mentioned 5 additional patients who had come under their observation and who had scleroderma and constricting lesions in the lower part of the esophagus.

In 8 of the cases reported in the literature esophagoscopy examination was performed, and, as noted previously, stenosis of the lower part of the esophagus was found in 5 of these cases. In the remaining 3 cases changes were noted in the lining of the esophagus. Ehrmann<sup>3</sup> noted thickening of the esophageal wall. Schwaiz<sup>16</sup> described esophagitis. Lindsay, Templeton and Rothman<sup>11</sup> found inflammatory changes in the lower two thirds of the esophagus, with a diffuse white membrane in the lower part of the esophagus, about 4 or 5 cm above the diaphragmatic level.

The dermatologic diagnosis in all of the 32 cases reported in the literature was scleroderma. No attempt was made to distinguish diffuse scleroderma from scleroderma occurring in association with Raynaud's syndrome (acrosclerosis). Twenty-seven of the reports of cases were presented in sufficient detail to enable one to classify the type of dermatosclerosis. In 21 of the cases vasomotor symptoms affecting the upper extremities had been noted prior to the onset of the cutaneous lesions. These cases may be classified as instances of acrosclerosis. Generalized scleroderma was apparently present in 4 cases, acute edematous scleroderma in 1 case and localized scleroderma in the remaining case.

An outstanding contribution to the study of the esophageal lesions of the sclerodermic diseases was made by Hoesli<sup>17</sup> in the thesis for his doctor's degree in 1937. Hoesli presented data on 3 cases which had been studied thoroughly and reviewed the literature in detail. Lindsay, Templeton and Rothman<sup>11</sup> have presented an excellent discussion of the subject, with the report of 5 cases. Weiss and his collaborators<sup>2</sup> have presented data on 2 cases of esophageal lesions in a paper that was concerned primarily with the cardiac manifestations of scleroderma.

Recently Hale and Schatzki<sup>18</sup> reported a series of 22 cases of scleroderma in which there were roentgenologic changes attributable to the disease. In 13 of these cases there was evidence of retardation of the passage of barium through the lower part of the esophagus. Data on 4 of these cases were presented in detail. In 1939 Ochsner and DeBailey<sup>19</sup> called attention to the presence of esophageal obstruction in 1 of their cases of scleroderma.

#### ANALYSIS OF EXPERIENCE OF MAYO CLINIC

The records of all patients seen at the Mayo Clinic from 1930 to 1943, inclusive, for whom diagnoses of scleroderma or acrosclerosis had

TABLE 2—Data Concerning Thirty-Six Cases of Acrosclerosis or Scleroderma in Which There Were Esophageal Signs or Symptoms

I 18 cases with positive roentgenographic or endoscopic observations	
A	Age distribution 34 to 61 years
B	Sex female 13, male 5
C	Dermatologic diagnosis acrosclerosis, 18
D	Roentgenologic diagnosis, 18 cases
	1 Esophageal dilatation or cardiospasm, 6
	2 Hiatal hernia, 9
	3 Negative results of examination, 3*
E	Esophagoscopic diagnosis, 8 cases
	1 Hiatal hernia (corroborated roentgen diagnosis), 3
	2 Sclerodermic involvement in patient with esophageal dilatation (by roentgen study), 1
	3 Sclerodermic involvement of esophageal wall not shown by roentgenologic examination, 2
F	Passage of sounds, 7 cases
	1 Diagnosis and treatment of cardiospasm, 3
	2 Dilatation of stricture associated with hiatal hernia, 4
II 6 cases with negative roentgenographic findings and no endoscopic studies	
A	Age distribution 23 to 60 years (average 44)
B	Sex female 2, male 4
C	Dermatologic diagnosis acrosclerosis 4, scleroderma 2
III 12 cases with neither roentgenographic nor endoscopic studies	
A	Age distribution 17 to 66 years (average 35)
B	Sex female 9, male 3
C	Dermatologic diagnosis acrosclerosis 11, scleroderma (acute) 1

\* In 2 of these cases esophagoscopic examination demonstrated changes in the esophageal wall. In the remaining case a diagnosis of cardiospasm was made by passage of sounds.

been made were reviewed. These records were studied with respect to the occurrence of esophageal symptoms or signs. In 36 of approximately 350 cases of scleroderma or acrosclerosis reviewed, dysphagia occurred or lesions of the esophagus were demonstrated (table 2). Roentgenographic studies were performed in 24 cases, and esophagoscopy examination was performed in 8 of these cases.

This study is concerned primarily with 18 cases in which conclusive roentgenographic or endoscopic observations were made. Reports

18 Hale, C. H., and Schatzki, R. The Roentgenological Appearance of the Gastrointestinal Tract in Scleroderma, *Am J Roentgenol* **51**: 407-420 (April) 1944.

19 Ochsner, A., and DeBailey, M. Scleroderma Symposium, Surgical Considerations, New Orleans: M & S J **92**: 24-30 (July) 1939.

16 Schwarz, P. Sklerodermie und Röntgenkastration, *Schweiz med Wchnschr* **56**: 246-248 (March) 1926.

17 Hoesli, H. Troubles fonctionnels et lésions de l'oesophage dans la sclerodermie, Thesis, Paris, Jouve & Cie, 1937.

of these 18 cases are presented briefly. The symptoms of Raynaud's syndrome preceded or were coincident with the development of cutaneous manifestations in all 18 cases. In all these cases the diagnosis was acrosclerosis. Table 3

TABLE 3—*Patients Who Had Dysphagia but Negative Roentgenographic Examination and with No Endoscopic Studies*

Age, Years	Sex	Dermatologic Diagnosis
45	F	Acrosclerosis
55	M	Acrosclerosis
40	M	Scleroderma *
60	M	Scleroderma
23	M	Acrosclerosis
39	F	Acrosclerosis

\* This case was reported by Pugh, Kvale and Marquies (Proc. Staff Meet., Mayo Clin. 20:410 [Oct. 31] 1915). Changes in the intestine which were characteristic of scleroderma were recognized by roentgenoscopic examination.

presents data for 6 patients who complained of dysphagia but for whom the results of roentgenographic studies were inconclusive and for whom no endoscopic studies were made. Twelve patients had dysphagia, but no roentgenographic or endoscopic studies were made (table 4).

TABLE 4—*Patients Who Had Dysphagia But No Roentgenographic or Endoscopic Studies*

Age, Years	Sex	Dermatologic Diagnosis
18	F	Acrosclerosis
31	F	Acrosclerosis
40	F	Acrosclerosis
31	F	Acrosclerosis
40	F	Acrosclerosis
37	F	Acrosclerosis
32	F	Acrosclerosis
35	M	Acrosclerosis
38	M	Acrosclerosis
66	F	Scleroderma (acute)
41	M	Acrosclerosis
17	F	Acrosclerosis

**Roentgenographic Observations**—Conclusive roentgenographic features were demonstrated in 15 cases. Esophageal dilatation with atony of the esophageal musculature was noted in 6 instances (cases 8, 9, 10, 11, 12 and 18). Peristaltic movements were decreased or absent in these cases. Apparent spasm at the cardia, with obstruction, was noted in 4 of the 6 cases (cases 9, 10, 11 and 12), and the passage of the barium meal was slower than normal in these cases. No studies were made of this group in the dorsal decubitus position. A roentgenoscopic diagnosis of cardiospasm was made in these cases.

In 9 cases (cases 1, 2, 3, 4, 5, 6, 7, 16 and 17) a diagnosis of esophageal hiatal hernia was made. In these cases part of the stomach was found to be above the level of the diaphragmatic hiatus. The herniated portion of the stomach was distinguished readily from the phrenic ampulla of the esophagus. The patients were studied roent-

genoscopically in both the upright position and the dorsal decubitus position. The passage of barium through the esophagus was slower than normal in each instance. In 2 of the cases (cases 3 and 5) there was obvious dilatation of the esophagus, giving the appearance of associated cardiospasm. In 6 of these 9 cases (cases 1, 2, 3, 4, 16 and 17) the hernia was definitely of the short esophagus type, and there was an associated stricture of the lower part of the esophagus and esophagogastric junction.

Roentgenographic studies were made in an additional 9 cases, but results were reported as negative. No attempt was made to study these 9 patients in the dorsal decubitus position or to carry out the elaborate time studies advised by Kure and his associates.<sup>8a</sup> It is probable that the time required for the passage of barium would have been found to be prolonged if Kure's technic had been used.

**Endoscopic Observations**—Esophagoscopy examination was performed in 8 cases. In 5 of these cases, a previous diagnosis of esophageal hiatal hernia had been made by roentgenographic means. The diagnosis of hiatal hernia was confirmed in each instance. Strictures were observed in 2 cases (cases 2 and 3) in association with hernias of the short esophagus type. The obstructions in both cases appeared to be the result of inflammation. In 2 other cases (cases 4 and 5), ulceration was noted at the esophagogastric junction. In 1 case (case 6) no ulceration was seen. In all these cases the gastric mucosa of the hernia could be visualized. Specimens were removed for biopsy in 3 of these 5 cases (cases 2, 3 and 4)—that is, in the 2 cases in which there were strictures and in 1 case in which there was severe ulceration of the lower part of the esophagus. The tissues removed disclosed inflammatory changes so great that it was not possible to detect sclerodermatous changes. In one of the strictures definite gastric mucous membrane could be demonstrated (case 3).

In 1 case (case 18) in which diffuse dilatation of the esophagus without obstruction at the cardia was described roentgenographically, the esophagoscopy picture was that of severe atrophic esophagitis. In the remaining 2 cases in which esophagoscopy examination was performed, roentgenography had shown nothing abnormal. The evidence in 1 case was minimal (case 15). The mucosa was pale and smooth but otherwise normal. In the other case (case 14) there were severe induration and thickening of the wall of the upper part of the esophagus. The changes appeared to be due to a sclerodermatous process.

Esophagoscopic examination of patients who have scleroderma is often extremely difficult. If general anesthesia is employed, the procedure is much less formidable than in other circumstances. Pentothal sodium administered intravenously provides satisfactory anesthesia. This drug was used in almost all the cases in our series in which esophagoscopic examination was performed.

*Passage of Esophageal Sounds*—In 7 of the 18 cases in which roentgenographic or endoscopic evidence was conclusive, esophageal sounds were passed over previously swallowed threads. Considerable information concerning the nature of the obstructing lesions in the esophagus can be obtained from the passage of sounds. In 1 case (case 13) a diagnosis was made of cardiospasm even though roentgenographic studies failed to reveal any obstruction at the cardia. Dilatation was performed for cardiospasm in 3 cases (cases 9, 10 and 13) and for relief of dysphagia due to the stricture associated with short esophagus in another 4 cases (cases 1, 2, 3 and 16). Relief or partial relief was obtained in all these cases, although recurrence of dysphagia at a later date was fairly common.

*Symptomatology*—In 34 of the 36 cases under consideration a history of dysphagia could be obtained. Most frequently the sense of obstruction was localized by the patient to the lower part of the esophagus. A few patients complained of a sense of a lump in the upper part of the esophagus or even in the hypopharynx. Those patients whose difficulty in swallowing consisted in difficulty in getting the food off the back of the tongue because of fixation of the oral structures were excluded from this series. In some cases the difficulty in swallowing was intermittent. In other cases the dysphagia was constant and progressive. Variations of the degree of dysphagia frequently suggested that esophageal spasm was superimposed on an organic obstruction.

Pain and burning on swallowing occurred in some cases. More commonly patients complained of substernal burning an hour or more after eating or especially when they would lie down. Frequently this distress was accompanied with epigastric pain, often extending to the back. Sometimes these symptoms were relieved by the ingestion of sodium bicarbonate or other antacid preparations.

The vasomotor phenomena associated with acrosclerosis almost invariably preceded the esophageal symptoms. In most instances the sclerodermatous changes also preceded the dys-

phagia or substernal burning. Rarely the esophageal disturbance was responsible for the symptom of which the patient complained primarily (cases 3, 4 and 18). Actually the esophageal disturbance was most often a delayed manifestation of the disease. This observation is in accordance with those of Hoeshli,<sup>17</sup> who reviewed all reported instances of esophageal disturbance in association with scleroderma up to 1937.

*Prognosis*—As O'Leary and Waisman<sup>20</sup> have pointed out, the prognosis of acrosclerosis is considerably more favorable than that of diffuse scleroderma. Many of these patients had had vasomotor symptoms for some years prior to the onset of cutaneous lesions. Esophageal lesions tend to occur in cases of advanced acrosclerosis. The occurrence of esophageal difficulties is often a bad prognostic sign. However, in some of our cases (cases 1, 2, 5, 7 and 13) there was definite evidence that the dermatologic process had been arrested. Diffuse scleroderma is almost invariably progressive. The prognosis of the esophageal lesion is usually determined by the progress of the primary disease. In many cases acrosclerosis appears to be self limited. In these cases the esophageal symptoms are not difficult to control.

*Treatment*—It is not the province of this report to discuss the treatment of acrosclerosis or scleroderma. However, the treatment of the esophageal lesion does merit consideration. When the esophageal difficulties are obstructive, temporary relief can be obtained almost invariably by dilatation of the esophagus with sounds over a previously swallowed thread. This method of treatment has been used both in the group of cases in which there was spasm at the cardia and in that in which there was stricture of the lower part of the esophagus associated with short esophagus and intrathoracic stomach. The 41 and 50 French sounds are used to dilate the cardia in those cases in which there is cardiospasm. In cases of cardiospasm associated with acrosclerosis or scleroderma, hydrostatic dilatation is not advisable. Sometimes the passage of the esophagoscope alone is enough to relieve the dysphagia of patients suffering from acrosclerosis (cases 5, 6 and 14). The selection of sounds for use in dilating the esophageal strictures depends on the degree of obstruction and the firmness of the lesion. Usually 29, 37 and 45 French sounds may be passed successively in these cases. It is not advisable to use sounds

20 O'Leary, P. A., and Waisman, M. Acrosclerosis, *Arch Dermat & Syph* 47: 382-397 (March) 1943.

larger than the 45 French sound in dilating organic lesions of the esophagus

Frequently, repeated passage of sounds is necessary to maintain an adequate esophageal lumen. In 1 of our cases (case 1) in which the esophagus was shortened and a stricture was present, dilation was performed on thirty-two occasions from 1926 to 1941, inclusive. Frequent dilation was necessary in the early stages. However, the intervals have become progressively longer and in recent years the patient has had little difficulty in swallowing.

#### COMMENT

In this study it was apparent that esophageal disturbances occur almost exclusively in cases of acrosclerosis rather than in those of generalized or diffuse scleroderma. It is not our purpose to discuss here the dermatologic differential diagnosis between these syndromes. However, it should be pointed out that the cutaneous lesions of acrosclerosis are confined to the hands, forearms, neck and upper part of the thorax, while diffuse scleroderma may involve the entire skin or the trunk, arms and hands. The facial lesions of acrosclerosis are likely to involve the oral cavity and to spread to the esophagus. When esophageal lesions are encountered in diffuse scleroderma, it is usually in those rare cases in which the scleroderma is cephalic in origin. Hence esophageal lesions are likely to occur in those cases in which there is early involvement of the face.

The constant association of Raynaud's phenomena with acrosclerosis suggests that a disturbance of the autonomic nervous system may be involved in the pathogenesis of acrosclerosis. Inasmuch as an imbalance between parasympathetic and sympathetic innervation is reputed to be a factor in the production of cardiospasm and other functional disturbances of the esophagus, it may be inferred that some common etiologic factor exists for the vasomotor, dermatologic and esophageal disturbances observed in acrosclerosis. Unquestionably, visible alterations of the lining of the esophagus have been demonstrated in the course of necropsy as well as at esophagoscopy examination in many of the cases of acrosclerosis. These changes are comparable both grossly and microscopically to those observed in the skin. However, there have been a considerable number of cases in which the esophageal lining appeared normal or nearly normal. It is postulated, therefore, that both organic changes in the walls of the esophagus and disturbances of its innervation may be

involved in the disturbed function of the esophagus.

Obstruction to the passage of food is the most common esophageal symptom of which patients suffering from acrosclerosis complain. It is apparent from the records that these patients may have either organic lesions in the esophagus or disturbances of function. As has been pointed out by Kurié,<sup>21</sup> by Weissenbach<sup>22</sup> and by Lindsay,<sup>11</sup> and their respective associates, disturbances of the motility of the esophagus may be demonstrated fairly early in the course of the disease. By the aid of a stop watch, delay of the passage of barium may be detected before the patient complains of dysphagia. The next change that is observed is a decrease or absence of the normal peristaltic movements of the esophagus. Normally the muscular activity of the esophageal wall is responsible for the rapid passage of food into the stomach. The peristaltic movements normally propel the food through the esophagus, and the cardiac sphincter opens in response to peristaltic waves. In the absence of muscular activity in the esophagus, gravity causes the food to pass slowly into the stomach. The greatest obstruction is at the cardiac sphincter, because there has not been any peristaltic wave to inhibit its action. In cases of more advanced acrosclerosis, gaping and ultimately dilatation of the esophagus take place.

Cardiospasm or achalasia of the esophagus may be defined as a dilatation of the esophagus in association with a nonorganic obstruction at the cardia. Cardiospasm is primarily a disturbance of the function of the esophageal musculature. This dysfunction is probably due to an imbalance of the autonomic innervation of the esophagus. The explanation for the functional esophageal disturbances in acrosclerosis is similar to that of cardiospasm except for the fact that in at least some instances sclerodermic changes in the esophageal wall are responsible for inadequate muscular activity. In other cases of acrosclerosis changes in the esophageal wall are not demonstrable, and it is possible that disturbances of the autonomic nervous system are a factor in such cases. The occurrence of esophageal troubles after the onset of the vasomotor disturbances in the upper extremities and sometimes either before or coincident with cutaneous

21 Kure, K., and Hiyoshi, J. Sklerodermie mit Muskeldystrophie, *Ztschr f d ges Neurol u Psychiat* 156: 36-44, 1936. Kure, Yamagata, Tsukada and Hiyoshi.<sup>8a</sup>

22 Weissenbach, R. J., Stewart, W., and Hoesli, H. Les troubles fonctionnels oesophagiens et les lésions de l'oesophage dans la sclerodermie, *Bull Soc franç de dermat et syph* 44: 1060-1063 (June 10) 1937.

lesions suggests that the origin of the entire syndrome possibly may be in the autonomic nervous system

The occurrence of hiatal hernia in association with acrosclerosis is more difficult to explain than that of cardiospasm. The characteristic "hidebound" appearance of patients suffering from acrosclerosis and scleroderma is due to the contraction of the skin over the affected parts. When sclerosis takes place in the connective tissue of the esophageal wall it is probable that there is an actual shortening of the esophagus. The cardiac portion of the stomach is pulled up into the thorax through the hiatus of the diaphragm. The typical appearance of short esophagus with hiatal hernia may be produced.

At this point it is desirable to discuss briefly shortening of the esophagus as it occurs in persons who are otherwise normal. The roentgenographic appearance of hiatal hernia of the short esophagus type is characteristic. The lower part of the esophagus lacks redundancy. The anterior and left lateral angulation of the esophagus just above the diaphragmatic hiatus is absent. The herniated portion of the stomach above the diaphragm appears as a pouch, which sometimes is confused with the phrenic ampulla of the esophagus. In some instances the characteristic pattern of the gastric mucosa may be discerned on roentgenoscopic examination. At esophagoscopy the lower part of the esophagus is observed to be a straight tube. There is gaping of the lowermost portion of the esophagus, and the usual tonic closure between esophagus and stomach is absent. The dark red appearance of the gastric mucosa stands out in sharp contrast to that of the pale esophageal mucosa. If necessary, tissue may be taken from the esophagogastric junction in order to demonstrate conclusively that the gastric mucous membrane is present above the diaphragmatic hiatus.

With hiatal hernia of the short esophagus type, the sphincteric property of the cardia is no longer present. When the patient is in the recumbent position, gastric secretions freely regurgitate into the esophagus. The esophageal lining is unable to resist the digestive action of the gastric acids and enzymes. Inflammation and ulceration take place in the lower part of the esophagus. The patient often complains of substernal burning, especially when lying down. Alternate ulceration and healing in the lower part of the esophagus often result in strictures of this segment of the esophagus and of the esophagogastric junction. Actual ulceration in the hernial sac is much less common than in the esophagus. When ulceration is present in

the herniated gastric mucosa, it is usually traumatic in origin.

The organic stenosis that occurs with short esophagus is confused frequently with carcinoma of the lower part of the esophagus and with cicatricial stricture of the esophagus due to other causes. It must be borne in mind that repeated ulceration and scarring of the lower part of the esophagus result in progressive shortening of the esophagus. We are in agreement with Allison and his associates,<sup>23</sup> who have stated their belief that short esophagus is more often acquired than congenital in origin.

The foregoing considerations are applicable to all hiatal hernias of the short esophagus type, including those that occur in association with acrosclerosis. In this series, a roentgenologic diagnosis of hiatal hernia was confirmed in 5 cases by esophagoscopy. Gastric mucosa was identified readily above the diaphragmatic "pinchcock" in each case, and in 1 instance biopsy of tissue from the esophagogastric junction clearly revealed gastric mucosa. In 2 other instances biopsy was performed on tissue from regions denuded of mucosa in order to exclude neoplastic disease. The 5 cases illustrate the several stages of development, namely, simple hiatal hernia, hernia with ulceration of the esophagogastric junction and hernia with stricture of the lower part of the esophagus. One of our patients was observed at a later stage by Lindsay and his associates. At the time of our examination a hiatal hernia associated with severe ulceration was found, but no stenosis had occurred. When this patient was examined by Lindsay and his associates, they described a moderate degree of stenosis. Although Lindsay and his associates interpreted this lesion as a stricture of the esophagus above the phrenic ampulla, they did state that the mucosa below the stricture was darker than that of the esophagus and that the color approximated that of gastric mucosa.

It is of interest that in 2 of our cases the roentgenologist described the feature of cardiospasm in addition to those of hiatal hernia with intrathoracic stomach. The absence of normal muscular activity, the esophageal dilatation, the abnormal behavior of the cardiac sphincter and the shortening of the esophagus must all contribute to the esophageal disturbance. The sclerosis of the connective tissues of the esophagus must be considered the basic factor in the causation of the esophageal symptoms and signs.

23 Allison, P. R., Johnstone, A. S., and Royce, G. B. Short Esophagus with Simple Peptic Ulceration, *J Thoracic Surg* 12 432-457 (June) 1943.

Disturbances of the innervation of the esophageal musculature also may play an important part. The development of hiatal hernia associated with peptic ulceration of the lower part of the esophagus and resultant stenosis appears to be a secondary process.

#### REPORT OF CASES

**CASE 1**—The patient, a single woman aged 48, registered at the clinic on June 16, 1922. Her vasomotor symptoms had begun in 1909, but her cutaneous lesions, which involved her hands, feet and face, had not begun until 1918.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was evident that the esophagus was shorter than normal and that there were a hiatal hernia and a stricture at the esophagogastric junction. Esophagoscopy examination was not performed.

At the patient's first visit to the clinic her condition was recognized as a vasomotor type of scleroderma. Her esophageal symptoms began in 1923. Dysphagia consisted in obstruction to passage of food in the lower part of the substernal region. On thirty-two occasions from 1926 to 1941, inclusive, the stricture was dilated, the largest sound used being a 45 French sound. The dysphagia always was relieved by dilation, and as the years have passed the intervals between dilations have become increasingly longer. Bilateral cervicothoracic ganglionectomy was performed in June 1929. There was improvement after the operation, and scleroderma has not progressed.

**CASE 2**—The patient, a married woman aged 48, registered at the clinic on Nov 25, 1942. Her vasomotor symptoms had begun in 1919, her cutaneous lesions, which involved her hands, feet and face, probably had begun in 1941, and her esophageal symptoms had begun in March 1942.

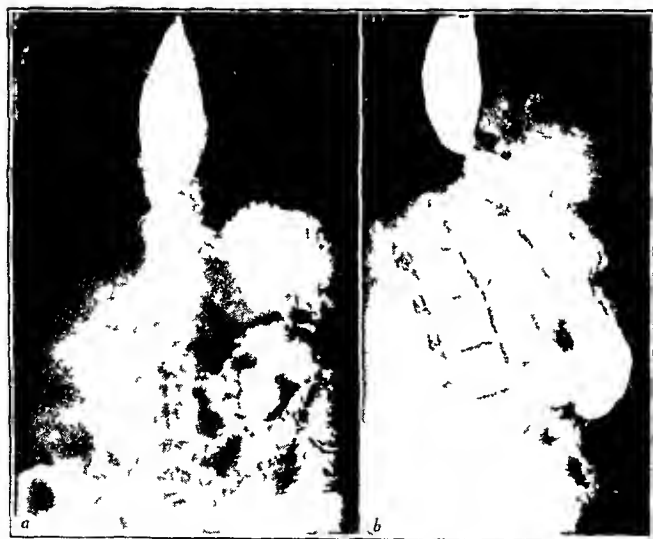


Fig 1—Esophageal hiatal hernia of short esophagus type with stricture at the esophagogastric junction with associated esophageal dilatation. (a) Anteroposterior view, (b) lateral view.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was evident that the esophagus was shorter than normal and that there were a hiatal hernia and a stricture at the esophago-

gastric junction. The esophagoscopy examination likewise showed a short esophagus with intrathoracic stomach and a stricture at the esophagogastric junction. At biopsy of tissue from the esophagogastric junction the tissue was observed to have been the site of inflammation.

The stricture was dilated, the largest sound used being a 45 French sound.

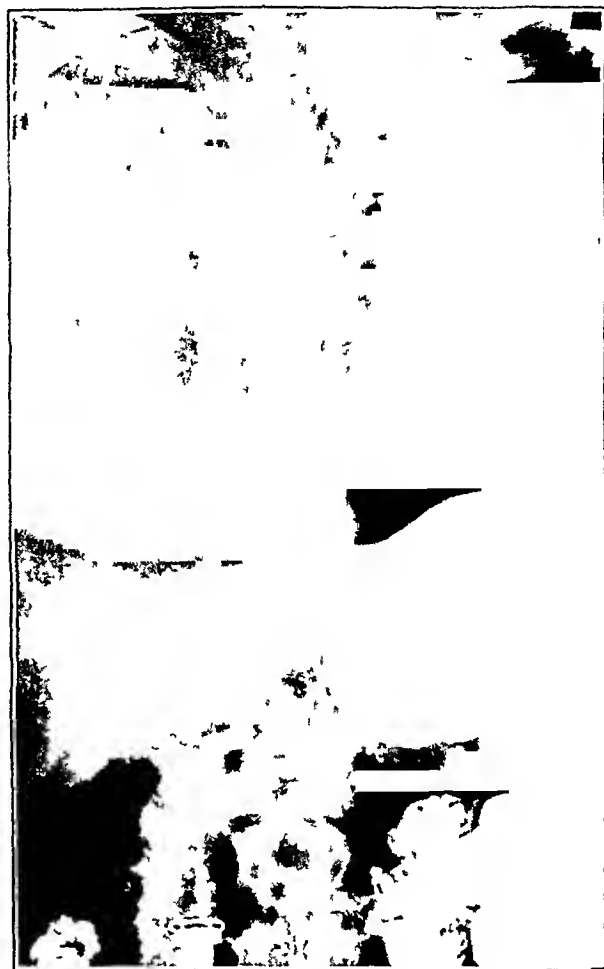


Fig 2—Hiatal hernia of the short esophagus type with about 2 inches (5 cm) of the stomach above the diaphragm. At esophagoscopy examination severe ulceration of the lower part of the esophagus and at the esophagogastric junction was observed. There was no dysphagia at the time of our examination. This patient was examined some time later by Dr Lindsay (Lindsay, Templeton and Rothman,<sup>11</sup> case 3). By this time a definite stricture had formed.

In this case there was a history of Raynaud's disease over a long period. The cutaneous changes had been recent and insidious in their onset. Dysphagia had been present for nine months when the patient came to the clinic. Dilation relieved the dysphagia. Bilateral cervicothoracic ganglionectomy was performed at the clinic. The patient returned for a recheck Aug 10, 1943. At that time her condition was definitely improved, and there was no dysphagia.

**CASE 3**—The patient, a married woman aged 61, registered at the clinic May 25, 1942. The vasomotor symptoms and the cutaneous lesions, which involved the hands, arms, face and thorax, had begun, apparently simultaneously, in 1938, but the esophageal symptoms, of which the patient complained primarily, had not begun until the autumn of 1939. Food had seemed to

stick in the lower part of the substernal region. Dilatation of the esophagus had given relief.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination showed cardiospasm with 1 inch (2.5 cm) of stomach above the diaphragm (fig 1). On esophagoscopy examination it was observed that there was esophageal hiatal hernia with secondary stricture at the esophagogastric junction. The mucosa was thin, and there were induration and fixation of the esophageal wall. The mucous membrane below the stricture was of the gastric type. On biopsy of a specimen of gastric mucous membrane, the tissue was observed to have been the site of inflammation.

The stricture was dilated on May 28, 1942 and on April 21, 1943, the largest sound used at each dilation being a 45 French sound. Dysphagia improved after each dilation. In November 1943, the patient's physician wrote that she was having trouble with her feet, with ulcers about the ankles.

**CASE 4** (reported by Lindsay, Templeton and Rothman as their case 3)—The patient, a man aged 46, registered at the clinic on July 27, 1942. His illness had begun in October 1940, with pain in the epigastrium and the lower part of the substernal region, chiefly at night. This was the symptom of which the patient complained primarily. The syndrome was typical of hiatal hernia. There was no dysphagia. The vasomotor symptoms had begun in January 1941, and the cutaneous lesions, which involved the hands, arms, abdomen and face, had begun in September of the same year. In other words, Raynaud's phenomena had preceded the cutaneous lesions.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination an esophageal hiatal hernia, with about 2 inches (5 cm) of stomach above the diaphragm, was observed. Otherwise, the stomach was normal (fig 2). Esophagoscopy revealed a hiatal hernia, with severe ulceration and erosion at the esophagogastric junction and in the hernial sac itself. Biopsy of removed tissue disclosed that the tissue had been the site of inflammation. Since there was no dysphagia, dilation was not performed.

**CASE 5**—The patient, a single woman aged 41, registered at the clinic on Aug 12, 1935. Her vasomotor symptoms had begun in 1929, and her cutaneous lesions, which involved her hands, feet and face, had begun in 1931. The esophageal symptoms had not begun at the time of her first registration. A dermatologic diagnosis of acrosclerosis was made. The condition, primarily Raynaud's syndrome followed by thickening of the skin, was more or less stationary from 1935 to 1943.

In August 1940, esophageal symptoms began. Dysphagia was intermittent and was suggestive of spasm. At times there was subxiphoid pain on swallowing. On roentgenographic examination in 1941, hiatal hernia with a small segment of the stomach above the diaphragm was observed. There was some indication of cardiospasm, but this was doubtful. Esophagoscopy disclosed a small hiatal hernia and ulceration at the esophagogastric junction.

Dilation was not performed. The esophageal symptoms were relieved entirely by the passage of the esophagoscope in 1941. The patient has not had any trouble since.

**CASE 6**—The patient, a married woman aged 62 years, registered at the clinic on Sept 14, 1943. Her vasomotor symptoms had begun in 1926, and her cutaneous lesions, which involved her hands, face and feet, had begun in 1933. In other words, a typical

Raynaud syndrome had preceded cutaneous involvement by several years. Esophageal symptoms had begun in 1939. They consisted in epigastric and substernal burning pain, symptoms typical of hiatal hernia. Nocturnal pain referred to the thoracic segment of the spinal column waked the patient from sleep. There was slight dysphagia at times.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination revealed an esophageal hiatal hernia with about 1 inch (2.5 cm) of stomach above the diaphragm. On esophagoscopy examination a small hiatal hernia was observed, but there was no ulceration. Dilation was not done.

**CASE 7**—The patient, a married woman aged 50, registered at the clinic on Nov 24, 1936. Raynaud's phenomena and dysphagia had begun in 1914 at about the same time. The dysphagia had been progressive,



Fig 3—Diffuse dilatation of the lower half of the esophagus. This suggests cardiospasm, but no definite obstruction at the cardia was demonstrated.

and the patient was able to swallow only liquids when she came to the clinic. The onset of the cutaneous lesions, which involved the hands and perhaps the face, was insidious and occurred about 1926. For nine years before her admission to the clinic the patient had had deposits of calcium in her finger tips and toes.

A dermatologic diagnosis of acrosclerosis was made. On roentgenologic examination a short esophagus with intrathoracic stomach and stricture at the esophagogastric junction was observed. Esophagoscopy examination was not done.

Bilateral thoracic sympathectomy was performed. The patient's dysphagia improved postoperatively, and therefore dilation was not done. According to letters of 1941, the results of sympathectomy were good.

**CASE 8**—The patient, a single woman aged 45, registered at the clinic on Oct 1, 1940. The vasomotor symptoms and the cutaneous lesions, which involved the hands, face and mouth, had begun at about the same time in 1929 or 1930. The patient had never had much dysphagia, but she had had substernal burning for years. The onset of this had been about 1930.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination disclosed diffuse dilatation of the lower half of the esophagus, which suggested cardiospasm, but no definite obstruction was observed (fig 3). Neither esophagoscopy examination nor dilation was done. No treatment was advised.

**CASE 9**—The patient, a man aged 40, registered at the clinic on July 16, 1941. Vasomotor symptoms had begun in 1938. Sensitivity to cold had developed a few months before the cutaneous lesions appeared in 1939. The latter involved the hands, face, neck, thorax and back. Scleroderma had advanced rapidly, and when the patient was seen at the clinic it was more or less generalized. The patient's condition was poor. Dysphagia, consisting of a sense of obstruction in the lower part of the substernal region and also at the cricoid level, had begun in 1940.



Fig 4—Cardiospasm with moderate dilatation of the esophagus in a case of acrosclerosis. (a) Anteroposterior view, (b) oblique view.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination cardiospasm with slight dilatation of the esophagus was observed. Esophagoscopy examination was not done.

Dilation relieved the dysphagia. The largest sound passed was a 50 French sound.

**CASE 10**—The patient, a man aged 55, registered at the clinic on July 3, 1943. His vasomotor symptoms had begun in 1929, and his cutaneous lesions, which involved his hands, feet, face, mouth and lips, had begun about 1931. Bilateral cervicothoracic ganglionectomy had been performed in July 1933. Esophageal symptoms had begun in 1936. There was obstruction to passage of food at the cardia. In 1937 roentgenographic examination had showed slight cardiospasm. In the same year dilation to a 60 French sound had relieved the obstruction, but there was a slight recurrence of obstruction in 1943.

A dermatologic diagnosis of acrosclerosis was made. When the patient was seen in August 1943, there was evidence of slight progression, especially in the face and mouth. Calcinosis of the fingers had developed.

Roentgenographic examination showed cardiospasm with moderate dilatation of the esophagus (fig 4). Esophagoscopy examination was not done.

**CASE 11**—The patient, a married woman aged 47, registered at the clinic on Oct 31, 1938. Vasomotor symptoms had begun in 1913, but cutaneous lesions had not begun until 1933. The latter, which involved the fingers, toes, face, shoulders and thorax, were slowly progressive. Rather vague dysphagia had begun about 1936.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination gave evidence of cardiospasm. Neither esophagoscopy examination nor dilation was performed. From subsequent correspondence there was not much change of the patient's status. In this case the condition was advanced.

**CASE 12**—The patient, a married woman aged 42, registered at the clinic on Aug 18, 1937. The vasomotor symptoms, a typical Raynaud syndrome, had begun in 1932. The cutaneous lesions, involving the hands, face and thorax, had begun in 1936. The skin of fingers and face became tightened.

A dermatologic diagnosis of acrosclerosis was made. Bilateral cervicothoracic ganglionectomy was performed, but the results were not good. About 1940 esophageal symptoms began. The patient described recurring episodes of obstruction to passage of food in the lower part of the esophagus. Roentgenographic examination in 1941 showed evidence of cardiospasm. In 1944 dilation was performed on two occasions to relieve dysphagia. Good results were obtained.

**CASE 13**—The patient, a married woman aged 61, registered at the clinic on June 6, 1933. Typical Raynaud's phenomena had begun in 1913. There had been ulceration of the finger tips and progression to the feet. The cutaneous lesions, which involved the hands, forearms, face, neck and feet, had begun in 1928. Dysphagia had begun at the same time as the cutaneous lesions, but it was intermittent. Food stuck above the cardia. The attacks of dysphagia came on suddenly, and sometimes complete obstruction persisted for twenty-four hours. The patient could feel the cardia open and food drop through.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination it was observed that the esophagus was normal but that a duodenal ulcer was present. Esophagoscopy examination was not performed. Dilation revealed and relieved spastic obstruction at the cardia. The largest sound passed was a 41 French sound.

The latest letter from the patient, dated 1935, two years after dilation, stated that the dysphagia had recurred but that the cutaneous lesions were stationary.

**CASE 14**—The patient, a married woman aged 44, registered at the clinic on Dec 9, 1942. Raynaud's phenomena had begun in October 1941, and cutaneous lesions, involving the hands, feet, face and thorax, had begun in May 1942. Esophageal symptoms had begun in July 1942. Pain and a sense of obstruction in the upper part of the esophagus were present on swallowing.

A dermatologic diagnosis of acrosclerosis was made. Roentgenographic examination showed that the esophagus and stomach were normal. On esophagoscopy examination thickening of the mucosa of the upper part of the esophagus and loss of elasticity of the esophageal wall were observed. These were interpreted as sclerodermic changes. Apparently there was some relief of the esophageal symptoms after passage of the esophagoscope, but subsequent progress has not been favorable.

CASE 15—The patient, a man aged 48, registered at the clinic on June 8, 1933. Typical Raynaud's phenomena of the hands had begun in October 1928, and their onset had been followed by sclerodermic changes of the hands in April 1929. Ulceration of the finger tips occurred. Later the sclerodermic changes had involved the face, feet and toes. Dysphagia, consisting of a sense of tightness in the throat, making swallowing difficult, had begun in 1930. Bilateral cervical sympathectomy in 1931 had produced temporary relief.

A dermatologic diagnosis of acrosclerosis was made. On roentgenographic examination a normal esophagus and stomach were observed. Esophagoscopy showed pallor of the mucous membrane but no changes of motility. Dilation was not done. Bilateral cervicothoracic

esophageal hiatal hernia of the short esophagus type, with about 2 inches (5 cm) of stomach above the diaphragm, was observed (fig 5). There was definite narrowing at the esophagogastric junction. There appeared to be associated spasm at the cardia. The pronounced thickening and rigidity of the mucosa of the esophageal entritus prevented a satisfactory esophagoscopic examination. Dilation was performed over a previously swallowed thread, and the stricture was dilated to a 43 French sound. Striking relief from dysphagia was obtained.

CASE 17—The patient, a married woman aged 34, registered at the clinic on Jan 21, 1941. In 1934 she had noted tingling and numbness in the fingers. In the ensuing few months cutaneous lesions had developed on hands, shoulders, neck and face. In 1936 deformities of the hands had appeared, and the sclerodermatous process had become more generalized. The dermatologic diagnosis was acrosclerosis with beginning involution and deposits of calcium in the finger tips.

There was no dysphagia at the time of the patient's first visit in 1941. Difficulty in swallowing developed within the next year and was rapidly progressive. Laparotomy was carried out elsewhere in 1942, and retrograde dilation of a stricture at the cardia was performed. This procedure was effective in relieving the dysphagia, and the patient has had little difficulty in swallowing since that time. When she returned to the clinic in 1944 severe destruction of the phalanges of both hands had occurred. Roentgenographic studies revealed a short esophagus with a short intrathoracic segment of stomach and narrowing at the esophagogastric junction. No peristaltic movements of the esophageal wall were noted.

CASE 18—The patient, a man aged 56, registered at the clinic on Sept 22, 1944. His vasomotor symptoms had begun in the spring of 1943, when he first noted pain and pallor of his hands and arms on exposure to cold. At the onset of his trouble swelling of his hands developed, but this symptom disappeared in the course of several months. He then noted stiffness in the skin of the face, neck and upper extremities. Dysphagia had been noted in May 1944, and this had been progressive.

A dermatologic diagnosis of acrosclerosis was made. Roentgenoscopic examination of the esophagus revealed diffuse dilatation with absence of peristaltic movements. No obstruction was detected at the cardia. Esophagoscopic examination was performed. The esophageal mucosa was found to be atrophic. There was no obstruction to the passage of the esophagoscope. Dilation was not carried out in this case. No further word has been received from this patient since his dismissal on Sept 29, 1944.

#### SUMMARY

Approximately 10 per cent of patients suffering from acrosclerosis or scleroderma made complaints referable to the esophagus. The most common complaint was dysphagia. Frequently there was also substernal burning after meals, especially when the patient was lying down.

Positive roentgenographic or endoscopic evidence was demonstrated in 18 cases. Dilatation of the esophagus similar to that seen in cardio-spasm was observed in 7 cases, and hiatal hernia with intrathoracic stomach was demonstrated in

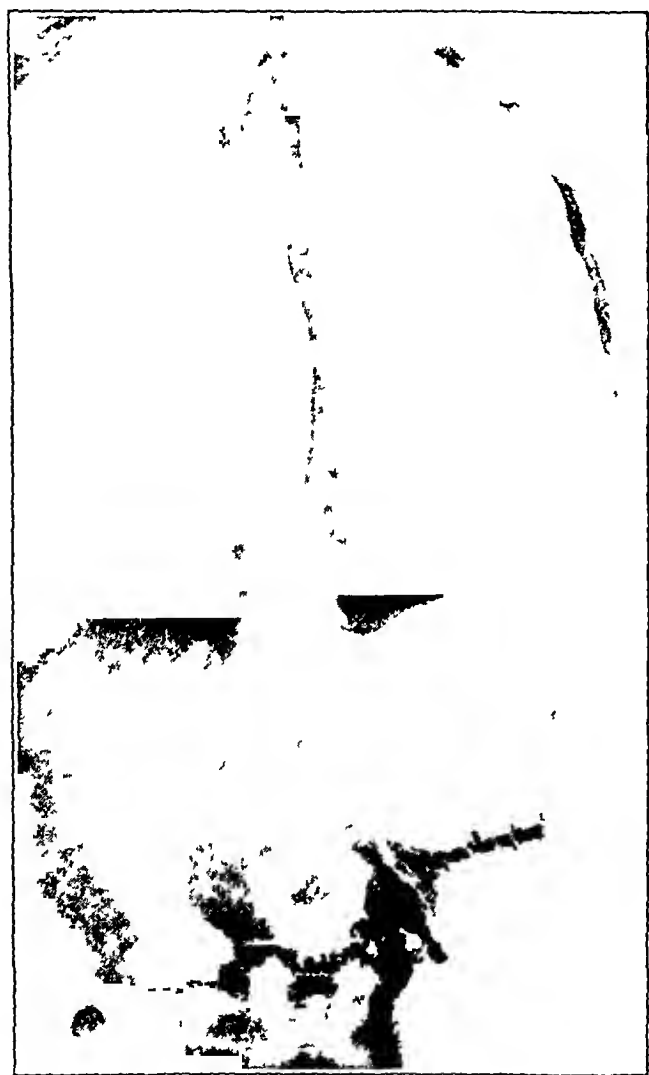


Fig 5—Short esophagus with hiatal hernia and stricture at the esophagogastric junction in a case of acrosclerosis.

ganglionectomy produced relief of the cutaneous symptoms for only a few months. The patient died in July 1935.

CASE 16—The patient, a married woman aged 39, registered at the clinic on May 15, 1944. Vasomotor symptoms had developed in 1939, and cutaneous lesions, which involved the hands, face and feet, had developed in the following year. Since 1941 there had been progressive dysphagia with obstruction to the passage of food in the lower part of the esophagus. The patient's diet had been restricted to fluids for three months prior to registration.

A dermatologic diagnosis of advanced acrosclerosis was made. On roentgenographic examination an

9 cases. In 2 other cases, sclerodermic changes were demonstrated in the esophageal wall.

Acrosclerosis should be distinguished from other forms of scleroderma. In acrosclerosis the phenomena of Raynaud's disease are present prior to the dermatologic changes or coincident with them. Thirty-three of the 36 patients who had esophageal symptoms presented the clinical syndrome of acrosclerosis. All the 18 patients for whom conclusive roentgenographic or endoscopic evidence was obtained had acrosclerosis.

The basic alteration in acrosclerosis and scleroderma is sclerosis of the connective tissues of the body. Sclerodermic changes in the connective tissues of the esophagus are chiefly responsible for the esophageal disturbances. It should be emphasized that esophageal disturbances are extremely uncommon in Raynaud's disease per se. Reduction or absence of muscular activity in the

wall of the esophagus and shortening of the esophagus apparently result from sclerodermic involvement. Disturbances of the autonomic nervous system may play some part in the causation. Clinical diagnoses of cardiospasm and hiatal hernia of the short esophagus type are made most frequently in these cases. Stenosis of the lower part of the esophagus and esophagogastric junction may occur with hiatal hernia as the result of chronic inflammation of the lower part of the esophagus. This inflammation is the result of incompetence of the cardiac sphincter with regurgitation of gastric secretions.

The treatment of the esophageal lesions of acrosclerosis consists of the passage of sounds over a previously swallowed thread. Fairly satisfactory results have been obtained. The esophageal stenosis of 1 of these patients has been treated satisfactorily over a sixteen year period by repeated dilations.

## NEUROLOGIC COMPLICATIONS DURING MENINGOCOCCIC MENINGITIS TREATED WITH SULFONAMIDE DRUGS

LIEUTENANT (JG) THOMAS W FARMER, MC-S, USNR\*

The purpose of this presentation is to outline the clinical course and prognosis in a variety of neurologic complications of meningococcic meningitis. During the epidemic years of 1942, 1943 and 1944, approximately 300 cases of meningococcic meningitis<sup>1</sup> were reviewed by me at four hospitals. About 100 cases involving children were included in this series. Of the 300 cases focal neurologic complications were observed to develop in 26 during the course of meningococcic infections. In each of these 26 cases it was ascertained that the paralysis did not exist before the onset of the meningeal infection and also that no other neurologic disease was present concomitantly with the meningitis. Detailed clinical information concerning the onset and severity of these sequelae was collected for this study.

An etiologic diagnosis was established in 24 of these 26 cases by the isolation of meningococci, group I, from the cerebrospinal fluid. In the remaining 2 cases presumptive diagnoses were based on the observations of meningeal signs, a petechial cutaneous eruption and purulent cerebrospinal fluid. All 26 patients received sulfonamide therapy. Sixteen received sulfadiazine, 7 were treated with sulfamerazine, 2 received sulfapyrazine, and 1 was treated with sulfathiazole. They all recovered.

The neurologic complications observed in these cases were of two groups: cranial nerve palsies and cerebral disorders. Since cranial

nerve palsies were much more common than cerebral complications, they are presented first.

### CRANIAL NERVE PARALYSES

Descriptions of involvement of cranial nerves in meningococcic meningitis occur in the earliest reports of the disease. Before serum treatment was instituted, in 1907, palsies of the sixth, seventh and eighth cranial nerves were repeatedly observed. Bilateral involvement of the auditory nerves with permanent deafness was well known as one of the serious complications in recovered patients. During the period of serotherapy, from 1907 to 1936, the same cranial nerve palsies were described. With chemotherapy reports of similar cranial nerve palsies have appeared. These palsies usually involve a single nerve or pair of nerves. Involvement of multiple cranial nerves rarely occurs.

### PARALYSIS OF THE SIXTH NERVE

Paralysis of the sixth cranial nerve with loss of function of the lateral rectus muscle prevents the eye from moving outward beyond the midline. Diplopia in the field of this paralysis is the result. Pseudoptosis of the eyelid on the side of the paralyzed muscle may be present. Abducens nerve palsy is the most common lesion of the extraocular muscles in meningococcic meningitis. It occurred frequently before the onset of serotherapy<sup>2</sup> and has remained common with serum and sulfonamide treatment<sup>3</sup>.

2 (a) Davis, A. E. Eye Symptoms of Cerebrospinal Meningitis, *M. News*, New York 86:644, 1905. (b) Hutinel, V., and Voisin, R. Maladies des meninges, in Gilbert, A., and Thoinot, L. *Nouveau traite de medecine et de therapeutique*, Paris, J. B. Bailliere et fils, 1912, vol. 35.

3 (a) Sinclair, W. The Ocular Complications of Cerebro-Spinal Fever, *Tr. Ophth. Soc. U. Kingdom* 39:233, 1919. (b) Neal, J. B. Epidemic Meningitis, in Abt, I. A. *Pediatrics*, Philadelphia, W. B. Saunders Company, 1925, vol. 6, chap. 158, p. 422. (c) McLean, S., and Caffey, J. P. Endemic Meningococcus Meningitis. The Clinical Manifestations in Infancy and in Early Childhood, *Am. J. Dis. Child* 35:357 (March) 1928. (d) Borovsky, M. P. A Clinical

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Dr. Derek Denny-Brown, Dr. Conrad Wesselhoeft and Dr. George Thorn, the chiefs of service at these hospitals, gave permission for the presentation of these cases.

1 These cases were studied at the Johns Hopkins Hospital in Baltimore and at the Boston City Hospital, the Massachusetts Memorial Hospitals (John C. Haynes Memorial) and the Peter Bent Brigham Hospital in Boston.

It occurs with similar frequency in children and in adults. The incidence of this complication has varied from 4 to 20 per cent in various epidemics, with an average of 10 per cent. Recently Harries<sup>3f</sup> reported strabismus in 15 per cent of 500 patients treated with sulfonamide drugs. Thus there has been no decline in the incidence of this complication as a result of sulfonamide treatment. Indeed, no decline should really be expected, since the sixth nerve is involved early in the course of the disease. In the majority of patients it is noted on the first physical examination after admission to the hospital.<sup>3c</sup> The involvement is most often unilateral. With recovery of the patient, the paralysis usually clears completely. Although the prognosis is good, rare cases of permanent abducens nerve paralysis have been noted.<sup>3a, d</sup> In such patients operative treatment, with ad-

tions when they were admitted to the hospital. Six of the patients presented relatively mild clinical pictures. All of these patients were conscious on entry to the hospital, and they complained of diplopia along with their meningeal symptoms. The other 3 patients were comatose. Seven of the patients had unilateral involvement, with partial or complete loss of function of one of the external rectus muscles. Two patients had complete bilateral sixth nerve paralysis. At the time of onset of paralysis the cerebrospinal fluid was purulent in every case, and usually it was under greatly increased pressure. All 7 patients with unilateral abducens nerve paralysis regained complete return of function of the nerve involved. In 5 of the 7 patients, function returned in less than two weeks. In the other 2 patients, recovery occurred in six and eleven weeks. Of the 2 patients with bilateral sixth

TABLE 1—Sixth Nerve Paralysis During Meningococcic Meningitis  
Nine Patients, Boston and Baltimore, 1912-1911

Case (Hospital)	Age, Years	Onset of Sixth Nerve Paralysis			Complete Recovery of Sixth Nerve Function
		Day of Patient's Meningitis	Unilateral or Bilateral	Cerebrospinal Fluid	
Case 1 (BOH)	21	1st	Unilateral	Purulent	11 weeks
Case 2 (JHH)	17	1st	Unilateral	Purulent	3 days
Case 3 (PBBH)	34	2d	Unilateral	Purulent	1 week
Case 4 (JHH)	19	2d	Unilateral	Purulent	2 weeks
Case 5 (JHH)	26	3d	Unilateral	Purulent	1 day
Case 6 (JHH)	56	3d	Unilateral	Purulent	6 weeks
Case 7 (JHH)	13	4th	Unilateral	Purulent	6 days
Case 8 (JHH)	29	3d	Bilateral	Purulent	8 months (right) 8 months (left)
Case 9 (JHH)	36	5th	Bilateral	Purulent	1 month (left) Not known (right)

vancement or resection of the external rectus muscle, may be advisable after diplopia has persisted for more than a year. However, the results are not uniformly successful.

In my study 9 patients with sixth nerve paralysis during meningococcic meningitis were carefully followed (table 1). The ages of the patients varied from 13 to 56 years. Paralysis developed early in the course of the meningeal infection. It appeared on the first to the fourth day in 8 patients and on the fifth day in 1. Weakness of the abducens nerve was noted in all 9 at the time of the patients' physical examina-

tion. In 6 patients with unilateral sixth nerve paralysis, 1 regained complete function of both external rectus muscles after eight months. The other regained complete function of the left abducens nerve one month after the onset of meningitis. However, paralysis of the right sixth nerve was still present at that time. Subsequent examination of this patient has been impossible.

The clinical picture of unilateral and bilateral abducens nerve paralysis is illustrated by 2 case histories.

Unilateral Paralysis of the Sixth Nerve

CASE 7—D S., a 13 year old Negro girl, was admitted to the Johns Hopkins Hospital on May 22, 1943 with stiff neck and chills of four days' duration. Four days before her admission severe headache and shaking chills developed. Milder headache persisted on the following day. Recurrent chills and stiffness of the neck developed on the day before her entry. On admission to the hospital she was complaining of severe headache, stiff neck and double vision.

Physical examination revealed a temperature of 103 F (rectally). The patient was drowsy and had a stiff neck and bilateral Kernig signs. There was complete

Study of Meningococcus Meningitis and An Analysis of One Hundred and Ninety Cases Observed in a Period of Eighteen Months, *Am J M Sc* **179** 82, 1930 (e) Lewis, P M. Ocular Complications of Meningococcic Meningitis. Observations in Three Hundred and Fifty Cases, *Am J Ophth* **23** 617, 1940 (f) Harries, G E. Cerebrospinal Fever. A Review of Five Hundred Cases Treated by Chemotherapy Without Intrathecal Serum, *Brit M J* **2** 423, 1942 (g) Keefer, C S. The Treatment of Bacterial Meningitis, *M Clin North America* **25** 1287, 1941

paralysis of the right external rectus muscle, with no other abnormal neurologic features

Lumbar puncture at the time of her admission yielded purulent cerebrospinal fluid under an initial pressure of 410 mm of fluid. The fluid contained meningococci, group 1. The patient received sulfamerazine therapy, and her temperature reached normal after three days. She continued to see double when she looked to the right. However, diplopia soon disappeared, and she regained full power of the right external rectus muscle six days after the onset of the nerve weakness. The meningeal signs disappeared at the same time, and she was discharged from the hospital in good health on June 4.

#### *Bilateral Paralysis of the Sixth Nerve*

CASE 8—S L, a 29 year old married white housewife, was admitted to the Johns Hopkins Hospital on March 12, 1942, with the complaints of headache and

#### PARALYSIS OF THE SEVENTH NERVE

Peripheral seventh nerve palsy results in loss of the function of all the muscles of facial expression on the affected side. This paralysis affects the forehead and eyelids as well as the musculature of the cheeks and mouth. With diplegia the face becomes masklike and motionless. The patient may also note a loss of the sense of taste on the anterior two thirds of the tongue as a result of interference of conduction through the chorda tympani.

Facial paralysis during the course of meningococcic meningitis has received only brief mention in the literature. An occasional reference to unilateral involvement of the seventh nerve ap-

TABLE 2—*Seventh Nerve Paralysis During Meningococcic Meningitis*  
Nine Patients, Boston and Baltimore, 1942-1944

Case (Hospital)	Age, Years	Day of Patient's Meningitis	Onset of Facial Nerve Paralysis		Recovery of Facial Paralysis
			Unilateral or Bilateral	Cerebrospinal Fluid	
Case 10 (MMH)	15	5th	Unilateral	Not examined that day	5 months, complete
Case 11 (MMH)	6	5th	Unilateral	Not examined that day	2 days, complete
Case 12 (PBBH)	16	10th	Unilateral	Clear	1 year, complete
Case 13 (JHH)	31	11th	Unilateral	Not examined that day	3 weeks, complete
Case 14 (JHH)	20	12th	Unilateral	Not examined that day	1½ years, incomplete
Case 15 (BOH)	22	9th	Bilateral	Clear	1 month, complete
Case 16 (MMH)	17	11th	Bilateral	Clear	3 months, complete
Case 17 (PBBH)	43	12th	Bilateral	Clear	1½ months, complete
Case 18 (JHH)	36	14th	Bilateral	Clear	1½ months, complete

fever of three days' duration. A sore throat had developed three days before her admission. On the next day she had a shaking chill, followed by headache, vomiting and a cutaneous rash. On the day of entry she complained of double vision. Her temperature was 102 F (rectally). She was cooperative and slightly drowsy and had stiffness of the neck and a positive Kernig sign. Examination of the cranial nerves revealed complete bilateral abducens nerve paralysis with pseudoptosis of the left eyelid (to prevent diplopia).

Lumbar puncture yielded purulent cerebrospinal fluid from which meningococci, group I, were grown on culture. She received sulfadiazine therapy, with prompt recovery from the meningeal infection. However, at the time of discharge from the hospital, on March 26, she was still complaining of double vision whenever she did not wear a patch over one eye. One month later examination revealed complete bilateral sixth nerve paralysis with diplopia. However, after several months she was able to move either eye outward to a slight degree. This ability increased, and her double vision soon disappeared. By November, eight months after her illness, she had regained complete function of both external rectus muscles.

peared before the advent of serum therapy. Also a few patients with this complication treated with serum or sulfonamide drugs have been reported on.<sup>4</sup> The incidence of facial palsy has been recorded as 1 to 5 per cent. However, no adequate description of the clinical course of this complication and no references to facial diplegia have been found in the literature on the subject.

Nine patients with peripheral seventh nerve paralysis after meningococcic meningitis were studied (table 2). The ages of the patients varied from 6 to 43 years. The course of the meningeal illness was relatively mild in 3 of the patients, while 6 had severe illnesses with delirium and coma. Weakness of the facial muscles developed from the fifth to the fourteenth day after onset of the meningeal signs and symp-

4 Hodes, H L, and Strong, P S. Treatment of Meningococcic Meningitis with Sulfonamides, *J A M A* 119:691 (June 27) 1942. Davis<sup>22</sup> Neal<sup>21</sup> Harries<sup>23</sup>

toms In 5 patients the paralyzes were unilateral, and in 4 facial diplegia developed For 5 of the patients the cerebrospinal fluid was examined on the day of onset of this complication, and in each of these cases it was found that the fluid was clear and contained less than 100 leukocytes per cubic millimeter For the other 4 patients the cerebrospinal fluid was not examined at the time of onset of the paralysis Thus, in this group of patients involvement of the seventh nerve developed late in the meningeal phase of the illness, at a time when the cerebrospinal fluid had already cleared Unilateral paralysis progressed to its maximum in one or two days However, in the development of complete facial diplegia, from one to four days elapsed in the spread from one nerve to the other In 2 of the 4 patients with bilateral seventh nerve palsy, loss of the sense of taste accompanied the paralysis

Complete follow-up studies of all 9 patients were obtained Recovery from facial paralysis was complete for 8 of the 9 Two of these patients regained function in less than one month, and for 6 complete recovery required from one to twelve months The ninth patient (case 14), in whom paralysis of the right seventh nerve developed, regained the ability to raise her right eyebrow and to close her right eye tightly seven months after the onset of her illness However, at that time her smile was still one sided This lower facial palsy persisted, and it was still present one and one-quarter years after the onset of meningitis

The report of 1 of the cases of unilateral seventh nerve paralysis is presented to illustrate the clinical picture of this complication The 4 cases of facial diplegia are briefly outlined All 4 of these cases are presented, because they follow such a characteristic clinical course, which apparently has not been described elsewhere

#### *Unilateral Paralysis of the Seventh Nerve*

CASE 12—D J, a 16 year old white schoolgirl, was admitted to the Peter Bent Brigham Hospital on June 11, 1942 She complained of abdominal pain, headache and vomiting of one day's duration On the day before entry she had a shaking chill followed by headache, vomiting and pains in her wrist and knee joints On admission she complained of abdominal pain and stiff neck Three weeks before entry she had an acute suppurative otitis media on the right side, which cleared completely in one week

Physical examination on her admission revealed a temperature of 100 F (rectally) She was disoriented and confused Stiff neck and Kernig's sign were present No motor, sensory or reflex abnormalities were present and no abnormalities of the cranial nerves

Lumbar puncture yielded purulent cerebrospinal fluid containing meningococci Treatment with sulfadiazine

was instituted, and the meningeal signs and symptoms disappeared in four days On the tenth day after the onset of meningitis the patient noted that she was unable to smile on the right side of her face She could not wrinkle the right side of her forehead A pronounced right seventh nerve paralysis had developed with no other neurologic abnormalities One month later the patient was able to wrinkle her forehead slightly on the right side Complete return of function of the facial muscles required one year

#### *Bilateral Paralysis of the Seventh Nerve*

CASE 15—C M, a 22 year old white married housewife, was admitted to the Boston City Hospital on Sept 19, 1942 She complained of severe headache, stiff neck and vomiting of two days' duration She felt nauseated two days before entry Nausea was followed by shaking chills On the following morning a severe headache developed Later in the day her neck became stiff, and she vomited On the day of her admission to the hospital her headache and stiff neck grew worse Her temperature was 101 F (orally) She was slightly drowsy, with an extremely stiff neck and positive Kernig sign No motor, sensory or reflex abnormalities were present and no abnormalities of the cranial nerves

Lumbar puncture done at the time of her admission revealed purulent cerebrospinal fluid containing meningococci, group I Sulfadiazine therapy was instituted, and her temperature fell to normal within two days Her headache and stiff neck subsided by the fifth day, and she felt completely well On the ninth day after the onset of meningitis she first noted a feeling of stiffness on both sides of her face and loss of the sense of taste She was unable to raise her eyebrows, to close her eyelids, to smile or to show her teeth Tears ran down over both cheeks She was unable to distinguish salt and sugar placed on her tongue In brief, a complete facial diplegia had suddenly developed Examination of the other cranial nerves and of the sensory, motor and reflex systems showed no abnormalities Lumbar puncture at this time revealed clear cerebrospinal fluid containing 11 leukocytes per cubic millimeter One week after the onset of this bilateral seventh nerve paralysis, there was a flicker of movement in her eyelids and she was able to control the secretion of tears She was discharged on the eighteenth day in the hospital with a residual bilateral facial weakness She could close her eyelids against slight resistance, and she could move the right corner of her mouth The sensation of taste was still absent One month after the onset of the facial paralysis this patient returned for reexamination She was able to smile normally, to raise her eyebrows and to close her eyes tightly The sensation of taste had returned to normal There was complete recovery of function of both seventh nerves

CASE 16—E F, a 17 year old white youth, was admitted to the Haynes Memorial Hospital on June 17, 1943, with the complaints of headache and stiff neck of one day's duration Four days before his entry fever and malaise, followed by a cutaneous eruption, developed On the day before entry he complained of violent headache, vomiting and stiff neck He was admitted in a comatose state His temperature was 104 F (rectally) He was alternately delirious and comatose Stiff neck and positive Kernig sign were the only neurologic abnormalities

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing menin-

gococci. Sulfamerazine therapy was instituted. After seven days his temperature returned to normal, and his meningeal signs subsided. On the eleventh day after the onset of meningitis a peripheral right facial paralysis developed, with normal movement of the left side of the face. At this time a lumbar puncture revealed clear cerebrospinal fluid containing 100 leukocytes per cubic millimeter. Four days later left facial paralysis developed. His face was masklike owing to facial diplegia. The sensation of taste was normal. Improvement was rapid, and one week later he had already regained approximately 75 per cent of the sensation of the left side of his face and 50 per cent of the right. Recovery was complete in three months.

CASE 17—F. S., a 43 year old white man, a lathe operator was admitted to the Peter Bent Brigham Hospital on April 12, 1943 complaining of stiff neck and headache of two days' duration. Two days before his admission he had a shivering chill followed by headache, vomiting and a cutaneous rash. The headache and stiff neck persisted until his entry. His temperature was 101 F° (orally). He had a stiff neck, positive Kernig sign and moderate papilledema.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing meningococci, and sulfadiazine therapy was begun. Meningeal signs disappeared after five days. On the twelfth day after the onset of meningitis a complete bilateral lateral paralysis suddenly developed. The sensation of taste was normal. Lumbar puncture revealed clear cerebrospinal fluid containing 4 cells per cubic millimeter. Two weeks later there was noticeable improvement. He was able to close his eyes and to smile. However, he could not wrinkle his forehead. Function returned more rapidly on the right side. After one and one-half months recovery was complete.

CASE 18—E. N., a 36 year old white man, was admitted to the Johns Hopkins Hospital on Sept. 22, 1942, with the complaints of headache and vomiting of two days' duration. A sore throat developed two days before his entry. On the next day he had a headache and he vomited. He became lethargic and later semicomatose on the day of his admission. His temperature was 102 F°. He had an extremely stiff neck and bilateral Kernig sign. There were no other neurologic abnormalities.

Lumbar puncture done at the time of his entry revealed purulent cerebrospinal fluid containing meningococci. He was treated with sulfadiazine, and his meningeal infection subsided during the next five days. On the fourteenth day after the onset of meningitis a complete left facial paralysis developed. At this time lumbar puncture revealed clear cerebrospinal fluid containing 100 leukocytes per cubic millimeter. Two days later an additional right facial paralysis developed. With this facial diplegia he noted loss of the sensation of taste. He was unable to distinguish salt from sugar on either side of his tongue. Two weeks after the onset of facial palsy he could close both eyelids against slight resistance. He could wrinkle the left side of the forehead and smile on the right side of his mouth. Soon the sensation of taste returned. After one and one-half months the facial diplegia had completely cleared.

#### PARALYSIS OF THE EIGHTH NERVE

Destruction of the eighth cranial nerves with then cochlear and vestibular divisions results in deafness and unsteadiness in walking. In small

children permanent bilateral deafness results in deaf-mutism.

Permanent deafness is one of the serious complications of meningococcal meningitis. This deafness is a direct result of the meningitis, and it is not related to otitis media, which often accompanies this disease in children. Before the use of serum treatment the incidence of involvement of the eighth nerve among recovered patients ranged from 5 to 30 per cent in different epidemics. With serum therapy deafness followed meningitis in 2 to 25 per cent of cases, with an average of approximately 5 per cent.<sup>5</sup> Since sulfonamide therapy has been instituted, no noticeable decline in the average incidence of acoustic nerve palsy has occurred. The present frequency ranges from 2 to 6 per cent, with an average of 5 per cent.<sup>6</sup> Permanent bilateral deafness is more common among children than among adults. The onset usually occurs during the first week of meningitis.<sup>2b</sup> However, it may develop after recovery, when the cerebrospinal fluid is clear.<sup>7</sup> In 2 reported cases bilateral deafness developed two and one-half and three months after complete recovery from meningitis with serum treatment.<sup>2d</sup>

In the majority of cases eighth nerve paralysis is bilateral, although unilateral involvement does occur. In about two thirds of those patients with total deafness, there are concomitant disturbances of the vestibular apparatus.<sup>8</sup> Auditory nerve palsy is usually permanent, although there are occasional cases in which the patients have completely recovered hearing.<sup>6b</sup> Vestibular symptoms disappear rapidly in adults, but in children they may persist for a year or longer. In children under 8 years of age complete deafness usually results in deaf-mutism.<sup>2b</sup> Thus meningococcal meningitis is one of the common causes of deaf-mutism.<sup>9</sup> In older children and

5 Fraser, J. S., and Dickie, J. K. M. Meningitic Neuro-Labyrinthitis, *Proc Roy Soc Med (Sect Otol)* **13** 23, 1920. Borovsky.<sup>2d</sup>

6 (a) Memorandum on Cerebro-Spinal Fever Among Troops, Great Britain War Office, London, His Majesty's Stationery Office, June 30, 1942. (b) Beeson, P. B., and Westerman, E. Cerebrospinal Fever. Analysis of 3,575 Case Reports, with Special Reference to Sulphonamide Therapy, *Brit M J* **1** 497, 1943. (c) Harries.<sup>2f</sup> Hodes and Strong.<sup>1</sup>

7 McLean, S., and Caffey, J. P. Sporadic Meningococcus Meningitis. Sequelae Following Specific Serum Therapy in Infancy and Early Childhood, *J A M A* **87** 91 (July 10) 1926. Neal.<sup>2b</sup>

8 Politzer, A. Diseases of the Ear, ed 6, edited by M. J. Ballin, Philadelphia, Lea & Febiger, 1926.

9 Shambaugh, G. E., Hayden, D. B., Hagens, E. W., and Watkins, R. W. Statistical Studies of the Children in Public Schools for the Deaf, *Arch Otolaryng* **12** 190 (Aug) 1930.

in adults with complete deafness, speech disorders develop, and special training is required for these patients

Pathologic studies have shown that permanent deafness after meningitis is usually due to a neurolabyrinthitis<sup>10</sup> The infection passes along the subarachnoid space from the base of the brain to the internal auditory meatus and then along the nerves and vessels to the labyrinth. A variety of pathologic changes producing deafness have been studied. These include (a) hydrocephalus, (b) changes in the walls of the fourth ventricle, (c) purulent infiltration of the eighth nerve and (d) purulent labyrinthitis. The pathologic changes producing transient deafness with complete recovery have not been described.

Five patients with deafness after meningitis were studied (table 3). Four of these were

TABLE 3—*Eighth Nerve Paralysis During Meningococcic Meningitis*  
Five Patients, Boston and Baltimore, 1912-1914

Patient (Hospital)	Age, Yr	Deafness, Unilateral or Bilateral	Severity of Deafness	Permanence of Deafness	
				Duration of Follow Up	Recovery of Hearing
Case 19 (JHH)	33	Unilateral	Complete	1½ years	None
Case 20 (JHH)	6	Bilateral	Nearly complete	2 years	Minimal
Case 21 (BOH)	5	Bilateral	Complete	2 years	None
Case 22 (JHH)	1	Bilateral	Complete	2½ years	None
Case 23 (JHH)	7	Bilateral	Nearly complete	1½ years	Minimal

children from 1 to 7 years of age, and in all 4 of them bilateral involvement developed. Unilateral eighth nerve paralysis developed in a 33 year old woman. In 2 patients deafness was first observed on the third and on the seventh day after the onset of meningitis. In the other 3 the time of onset could not be accurately determined. In all patients deafness was complete or nearly complete. In 3 of the children unsteadiness in walking was noted after recovery. These 5 patients were all followed for periods of one and one-quarter to two and one-half years. In 3 patients there was no recovery of hearing at all, and in the other 2 recovery was minimal. An unsteady gait persisted for two years in 2 of the children, whereas 1 child walked normally one month after recovery. In addition, the children with bilateral deafness

acquired speech disorders. One infant, who had meningitis at the age of 1 year, was a deaf-mute at 3½ years of age. The other 3 children talked, but they spoke too fast to be understood. On returning to school they were no longer able to do satisfactory work. Therefore they are now attending special schools for the deaf. The late treatment of these otherwise normal children includes training in lip reading and voice in order that they may continue their intellectual development.

The clinical pictures of unilateral and bilateral eighth nerve paralysis are illustrated by the following 2 case histories.

#### *Unilateral Paralysis of the Eighth Nerve*

CASE 19—M. P., a 33 year old white married woman, was admitted to the Johns Hopkins Hospital on March 31, 1943, with the complaints of headache, vomiting and stiff neck of three days' duration. A headache had developed three days before her admission. This became more severe on the following day. A stiff neck and vomiting developed on the day of her admission. Her temperature was 99.8 F. She was delirious and had pronounced meningeal signs. No focal neurologic signs were elicited.

Lumbar puncture done at the time of her admission revealed purulent cerebrospinal fluid containing meningococci. She was treated with sulfamerazine. After her meningeal infection subsided, she complained of ringing in the right side of her head. Examination of the ears ten days after the onset of meningitis revealed complete loss of bone and air conduction in the right ear. However, the exact day of the onset of deafness was not known. For the next few months the deafness in the right ear remained unchanged. She was troubled with tinnitus and repeated "explosions in the head." These symptoms gradually subsided during the first year. On reexamination one and one-quarter years after the onset of meningitis she was still found to have complete deafness in her right ear with no other complaints.

#### *Bilateral Paralysis of the Eighth Nerve*

CASE 20—R. T., a 6 year old white boy, was admitted to the Harriet Lane Home at the Johns Hopkins Hospital on Oct. 3, 1942, with headache, stiff neck and convulsions of one day's duration. On the day before his entry he complained of a headache and stiff neck. He had a generalized convulsion. On the day of admission he became drowsy and confused. His temperature was 103 F. He was disoriented, and he had definite meningeal signs. Lumbar puncture done at the time of his entry revealed purulent cerebrospinal fluid containing meningococci. Treatment with sulfapyrazine was instituted. By the third day after the onset of meningitis he was much improved, and he recognized his visitors. However, he said that he was unable to hear them. Thus, during the early stage of this meningeal infection complete deafness had developed in his right ear and severe deafness in his left ear. One month later his hearing had improved slightly in the left ear, so that he was able to hear words shouted at him. However, he remained totally deaf in the right ear. His gait was slightly unsteady. On reexamination five months after the onset of deafness his hearing was found to be unimproved. Two

<sup>10</sup> Hagens, E. W. Pathology of the Inner Ear in a Case of Deafness from Epidemic Cerebrospinal Meningitis, *Ann. Otol., Rhin. & Laryng.* 49:168, 1940. Fraser and Dickie.<sup>5</sup> Politzer.<sup>8</sup>

years after his illness he was still completely deaf in the right ear and severely deaf in the left ear. Slight swaying in walking was still present.

### PARALYSIS OF OTHER CRANIAL NERVES

Involvement of the second cranial nerves with changes in the optic disks is common in meningococcic meningitis. Lewis<sup>11</sup> noted "papillitis" in 12 per cent of 350 cases. These changes are nearly always bilateral and subside with recovery of the patient. Rarely partial secondary atrophy of the optic nerve or blindness follows.

Partial third nerve paralysis with transient divergent strabismus<sup>12</sup> or ptosis<sup>12</sup> have occasionally been noted. In 1 patient I observed, complete left third nerve paralysis developed, with ptosis, dilated pupil and divergent strabismus, during the course of meningococcic meningitis. However this patient also had untreated syphilis of the central nervous system, so that the etiologic basis of the cranial nerve complication was uncertain.

Rare cases of fifth nerve paralysis<sup>13</sup> and of pharyngeal paralysis<sup>14</sup> during meningococcic meningitis have been described.

### CEREBRAL COMPLICATIONS

In patients with severe meningeal infections, abnormal mental states develop, including disorientation, confabulation, hallucinations, convulsions, tremors and coma.<sup>15</sup> In particular, persons chronically addicted to alcohol who have meningitis frequently present confusional psychoses, and they may be admitted to mental hospitals with the mistaken diagnosis of delirium tremens.<sup>16</sup> Approximately one third of children with meningitis have generalized convulsions<sup>17, 18</sup>. Such cerebral symptoms as these are part of the meningitic picture and are not regarded as cerebral complications of meningitis.

Hemiplegia and aphasia, however, represent definite cerebral involvement. These unusual complications were first reviewed in the French literature.<sup>19</sup> In 1898 Florand<sup>16</sup> described the

case of a 13 year old child in whom aphasia and right-sided hemiplegia developed on the twelfth day of meningitis. The cerebrospinal fluid was clear at that time, but the patient died on the following day. In another report<sup>16</sup> left-sided hemiplegia was said to have developed in a 17 year old patient twenty-three days after the onset of meningitis. At this time the cerebrospinal fluid was clear. Reexamination of the patient two months later revealed persistent spastic hemi-

TABLE 4—Cerebral Complications During Meningococcic Meningitis  
Three Patients, Boston City Hospital, 1942-1943

Patient Case	Age, Yr	Onset of Complication			Complete Recovery from Complication
		Day of Meningitis	Cerebrospinal Fluid	Clinical Picture	
Case 24	9	7th	Clear	Right sided convulsions	1½ hours
				Right hemi paresis	1 day
				Right homonymous hemianopia	1 month
				Aphasia	2 months
Case 25	9	6th	Not examined that day	Right-sided convulsions	4 hours
				Right hemi paresis	10 days
				Aphasia	4 months
Case 26	6	9th	Clear	Generalized convulsions	4 days
				Left hemi paresis	3 weeks

plegia. Recently Harries<sup>20</sup> noted 1 patient with transient hemiplegia among 500 patients with meningitis treated with sulfonamide drugs. Thus, focal cerebral complications in meningococcic meningitis do occasionally occur despite sulfonamide therapy. The pathologic process which produces this clinical picture is not known. However, it must be distinguished from brain abscess.

In my study 3 patients with meningococcic meningitis complicated by hemiplegia were observed (table 4). Two of these were children, each of whom was 9 years old. The third patient was a 65 year old man. These 3 patients were treated early in the courses of their infections, and they did not present unusually severe clinical pictures. One patient had only meningeal signs and symptoms on his admission to the hospital, 1 was irrational, and the third was comatose. The complication had its onset from the sixth to the

16 Castaigne, J, and Rivet, L. Ménigite cérébro-spinale epidémique compliquée d'hémiplégie. Comparaison chez un même malade des effets thérapeutiques de l'électrargol et du sérum de dopter, Bull et mem Soc med d hôp de Paris 27 900, 1909

11 Randolph, R. L. A Clinical Study of Forty Cases of Cerebro-Spinal Meningitis, with Reference to the Eye Symptoms, Bull Johns Hopkins Hosp 4 59, 1893

12 Neal<sup>17</sup> Borovsky<sup>18</sup> Harries<sup>20</sup>

13 Hoesch, K. Ueber epidemische Meningitis mit Encephalitis und über Menigo-Encephalitis (Encephalitis japonica), Zentralbl f inn Med 61 161, 1940

14 Weir, T. W. II, and Vautier, C. K. Mental Symptoms in Cerebrospinal Meningitis, Brit M J 1 179, 1942

15 Florand, A. Un cas de meningite cérébro-spinale epidémique, Bull et mem Soc mcd d hôp de Paris 15 530, 1898

ninth day after the onset of definite meningeal signs and symptoms. At this time the cerebrospinal fluid was already clear. The onset of this complication was heralded by a series of convulsions lasting from a few hours to a few days. In 2 patients seizures were unilateral, and in the third they were generalized. Convulsions left the patient with a hemiparesis of one to twenty-one days' duration. In 1 patient there was a complete homonymous hemianopsia, which gradually cleared during one month. In 2 patients an aphasic disorder developed, which disappeared in two to four months. In 1 patient right homonymous hemianopsia, hemiparesis and aphasia were associated with a definite slow wave focus in the left parieto-occipital area as observed by electroencephalogram. As the clinical symptoms disappeared, the electroencephalogram showed a less definite focus. This patient's aphasic disorder completely disappeared in two months. The electroencephalogram became normal after six months. In none of these patients have any sequelae developed from this cerebral complication. Neither of the children has had any convulsions during the first year after recovery.

The clinical course of 2 of these patients is presented here.

**CASE 24—J F**, a 9 year old white schoolboy in the third grade, was admitted to the Boston City Hospital on May 8, 1943, with the complaints of headache and vomiting of one day's duration. On the day before entry this boy came home from school because of headache, vomiting and fever. On the morning of admission he again vomited several times, and his neck and back became stiff. In a few hours he became comatose, and he was admitted to the hospital. Prior to his illness he had had no convulsions.

Physical examination on admission revealed an acutely ill boy with a temperature of 103 F (rectally). He was comatose. His jaws were closed tightly. His neck was extended and quite stiff. His legs were flexed at the knees, and they could not be completely extended. No motor, sensory or reflex abnormalities were noted and no abnormalities of the cranial nerves.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid from which meningococci were grown on culture. Sulfadiazine therapy was instituted. On the following day he recognized his mother, but headache, stiff neck and fever persisted. By the fifth day, his temperature had fallen to 99 F, the meningeal signs had diminished, and he looked much brighter. However, on the seventh day after the onset of meningitis he had a right-sided convulsive seizure with loss of consciousness. His head and eyes turned to the right with clonic movements of the right arm and leg for forty-five seconds. During this seizure he was incontinent of urine. This was followed by brief episodes of twitching of the right arm, which recurred at five minute intervals for the next ninety minutes. He was given phenobarbital subcutaneously, and the twitching soon ceased. It was observed that his right arm was weak. Lumbar puncture at this time revealed clear cerebrospinal fluid.

On the following day he was drowsy but cooperative. A mild aphasic disturbance was noted. For example, he was unable to name certain common objects (watch and buckle). He was unable to write many simple words. In attempting to write the alphabet he wrote "a, b, c" but no further. He could write his name, his address and certain numerals correctly. He could read words well, and he could carry out simple commands. In addition, it was noted that he had a definite right homonymous hemianopsia. There was no facial weakness and no weakness of the right arm or leg. An electroencephalogram at this time revealed a definite, large slow wave focus (3 per second) in the left parieto-occipital area. Two days later the boy was able to sit up, and he felt rather well. His aphasic disorder had improved. He was now able to write the alphabet, but he still misspelled simple words. The right homonymous hemianopsia remained nearly complete. However, within one month after the onset of this hemianoptic disorder his visual fields returned to normal. At this time, he still had some difficulty in writing words which had been familiar to him before his illness. During the next month he had to relearn the multiplication tables, his prayers, the use of capital letters and other parts of his previously collected knowledge. Two months after his illness he was again able to read and write normally. The electroencephalogram at this time revealed less pronounced abnormalities than previously. However, there were still bursts of slow waves, chiefly in the left occipital area. Subsequent electroencephalograms revealed a gradual return to the normal pattern in six months after his illness. He did satisfactory school work during the following year, and he had no episodes of unconsciousness or convulsions in this period.

**CASE 25—W S**, a 9 year old white schoolboy in the third grade, was admitted to the Boston City Hospital on March 17, 1943, with fever, headache and vomiting of two days' duration. A sore throat developed two days before his entry. The following day he complained of headache, backache and vomiting. On the day of entry he became irrational, with severe headache and vomiting. He thought that some one was stealing his sister from their home.

When this boy was 2 years of age, he had an infection of the left middle ear with mastoiditis. At this time a mastoidectomy on the left side was performed. During this illness no convulsive disorders were observed. However, during the following year he had four grand mal seizures, each one of ten to fifteen minutes' duration. These seizures ceased to occur after he was 3 years old, so that he had had no convulsions during the past six years.

Physical examination on his admission to the hospital revealed a temperature of 102 F (rectally). The left ear drum was perforated, and there was an old mastoidectomy scar. He was disoriented and irrational, with stiff neck and Kernig's sign. Examinations of the cranial nerves and of the motor, sensory and reflex systems revealed nothing abnormal.

Lumbar puncture done at the time of his admission revealed purulent cerebrospinal fluid containing meningococci. Sulfadiazine therapy was instituted. During the first three days he improved slowly. He became oriented, and his fever subsided. However, on the sixth day after the onset of meningitis he had a series of four convulsions, which involved the right side of his body. These seizures occurred over a four hour period, and they were followed by aphasia and right hemiparesis. On the following day, his temperature

was 99 F, and his hemiparesis and aphasic disorder had improved. A slight weakness of the lower right side of the face was noted. During the next ten days the right-sided weakness gradually disappeared. However, the aphasic disorder persisted. He named most common objects incorrectly. He was unable to write his name. He could write only the first seven letters of the alphabet. He was unable to read simple words. However, he was able to demonstrate the use of objects presented to him. One month after the onset of this aphasia he was still unable to name objects. However, he was able to write his name and the alphabet. He read letters but not words. During the next three months he learned to read and write again. Thus, four months after his illness he could read letters and words fairly well. He could write simple words correctly, and he could add, subtract and multiply. When he returned to school, his work was satisfactory. Subsequently he has had no convulsive seizures.

in the course of meningitis, when the cerebrospinal fluid is purulent. It is usually unilateral, and complete recovery within a few weeks is the rule.

2 Unilateral and bilateral seventh nerve paralyses are usually late complications, which develop after the cerebrospinal fluid has become clear. In 4 patients with facial diplegia this late onset of paralysis during convalescence was characteristic. Recovery of function usually requires several months. It is complete in most but not all of the cases.

3 Eighth nerve paralysis with deafness is the most serious cranial nerve complication. It occurs more commonly among children than

TABLE 5—Outline of the Clinical Features of Cranial Nerve Paralyses During Meningococcic Meningitis

Cranial Nerve Involved	Age	Incidence Reported at Present, per Cent	Unilateral or Bilateral	Onset of Complication		Usual Prognosis
				Stage of Meningitis	Cerebrospinal Fluid	
Sixth	All ages	5 to 15	Both, usually unilateral	Acute	Purulent	Complete, recovery in 1 to 4 weeks
Seventh	All ages	1 to 5	Both, usually unilateral	Convalescent	Clear	Complete, recovery in 1 to 12 months
Eighth	Usually children	2 to 6	Both, usually bilateral	Acute or convalescent	Purulent or clear	Permanent, deafness

#### SUMMARY

From the large group of possible sequelae occurring in patients with meningococcic meningitis, certain neurologic complications were selected for study. Twenty-six patients with focal neurologic abnormalities among a group of 300 patients with meningococcic meningitis were carefully followed during the past three years. This series included 9 patients with sixth nerve paralysis, 9 with seventh nerve paralysis, 5 with eighth nerve paralysis and 3 with transient focal cerebral complications.

Cranial nerve paralyses present characteristic clinical features. (The usual course of each one is outlined in table 5.)

1 Sixth nerve paralysis, the most common extraocular nerve palsy, usually develops early

among adults, and it usually is bilateral. Its present incidence is approximately 5 per cent. It may develop during the acute meningitic infection, convalescence or even after recovery. Deafness is permanent in the vast majority of cases. In young children deaf-mutism results. Occasional cases of transitory deafness also occur.

Cerebral complications with convulsions and transient hemiplegia occur rarely. They usually appear late in the course of the infection with clear cerebrospinal fluid. The convulsions may be unilateral or generalized. They are followed by hemiparesis with occasional aphasic disorders and hemianopsia. Electroencephalograms reveal focal disturbances in the area involved. All of these neurologic and electroencephalographic signs were observed to clear completely, with no residua.

# AN ACCOUNT OF STOCK

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Each state chairman of the Procurement and Assignment Service for Physicians is faced with the baffling task of keeping track of the migratory habits of his colleagues. Among other bits of information this entails on his part a knowledge of those of the medical profession who die at any time in any city or town within his area and of those by whom they are replaced. Hence it has happened that during my term of service as state chairman for Massachusetts I have perforce explored with increasing diligence a curious source for medical research—the obituary columns of *The Journal of the American Medical Association*.

In a representative issue more than seventy deaths may be reported. If one happens to be morbidly inclined, one suspects that vascular disease affecting either the heart, the kidneys or the cerebral vessels is a disorder to which the medical profession has special predisposition. In 1944, in the December 1 issue of *The Journal*, to take an offhand sample, seventy-one deaths were reported. There were thirteen deaths from coronary artery disease, sixteen from unspecified heart disease on an arteriosclerotic background, five from generalized arteriosclerosis in which the exact cause of death was not noted, four from cerebral hemorrhage or thrombosis, two from nephritis and one from myocarditis.

Records such as this, issue after issue, have interested many observers. Each year *The Journal* is likely to comment in an editorial on the annual cost of cardiovascular disease to our profession, and several clinicians have written about it. White,<sup>1</sup> for example, found among one hundred physicians examined for cardiac symptoms that seventy-six had organic disease of the heart or blood vessels. Willius<sup>2</sup> has called today's death rate from heart disease among physicians appalling. Falk<sup>3</sup> has expressed the view that coronary disease is taking a disproportionate toll each year from the ranks of the

medical profession, and Musser<sup>4</sup> appeared to agree with him. Smith,<sup>5</sup> approaching the problem from a slightly different angle, has shown that the incidence of coronary sclerosis among physicians who have consulted the Mayo Clinic was considerably higher than that among bankers, lawyers, clergymen or laborers, and Kellogg,<sup>6</sup> studying physicians and other candidates of comparable age who applied for Army commissions, also found that the incidence of heart disease, hypertension and renal disease was appreciably greater among physicians than among others.

Such observations are impressive. On the other hand, there is another side to the story. Ten years ago Riesman and Harris<sup>7</sup> pointed out that the increase in number of deaths reported from heart disease year by year is not a fortuitous happening but in reality represents a triumph of preventive medicine. For by the prolongation of the average span of life, more persons are kept alive to die from those diseases that naturally afflict advancing years. And Chadwick,<sup>8</sup> evidently thinking along similar lines, has predicted that the mortality from diseases of the heart and blood vessels is bound to increase so long as the average age of the population continues to lengthen.

It is possible, therefore, that the increasing incidence of vascular disease among physicians may be more apparent than real, is in many instances the price of longevity and is in no way remarkable. Since there are differing views on a matter of such general professional interest and since the rational conservation of medical manpower is at present so desirable, it seemed worth

4 Musser, J. H. *The Doctor's Heart*, Ohio State M. J. **40** 123-125 (Feb.) 1944.

5 Smith, H. L. *Incidence of Coronary Sclerosis Among Physicians*, J. A. M. A. **108** 1327-1329 (April 17) 1937.

6 Kellogg, F. *Physical Defects Among Physicians and Other Applicants for Commission*, Army M. Bull., July 1943, no. 68, pp. 158-165.

7 Riesman, D., and Harris, S. E. *Disease of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease*, Am. J. M. Sc. **187** 1-15 (Jan.) 1934.

8 Chadwick, H. D. *The Diseases of the Inhabitants of the Commonwealth*, New England J. Med. **216**. 1003-1015 (June 10) 1937.

1 White, P. D. *The Physician Himself*, J. A. M. A. **115** 1495-1499 (Oct. 26) 1940.

2 Willius, F. A. *A Talk on Cardiac Disease Among Physicians*, Proc. Staff Meet., Mayo Clin. **16** 714-716 (Nov. 5) 1941.

3 Falk, O. P. J. *Coronary Disease and the Doctor*, Illinois M. J. **80** 115-119 (Aug.) 1941.

while to attempt an account of stock The conclusions must be regarded as being of a preliminary nature For at the 1944 meeting of the House of Delegates of the American Medical Association the Board of Trustees<sup>9</sup> made the following statement

The deaths of physicians have continued at almost the same rate annually for many years The number varies from a high of slightly more than 3,700 in 1939 to nearly 2,900 in 1931

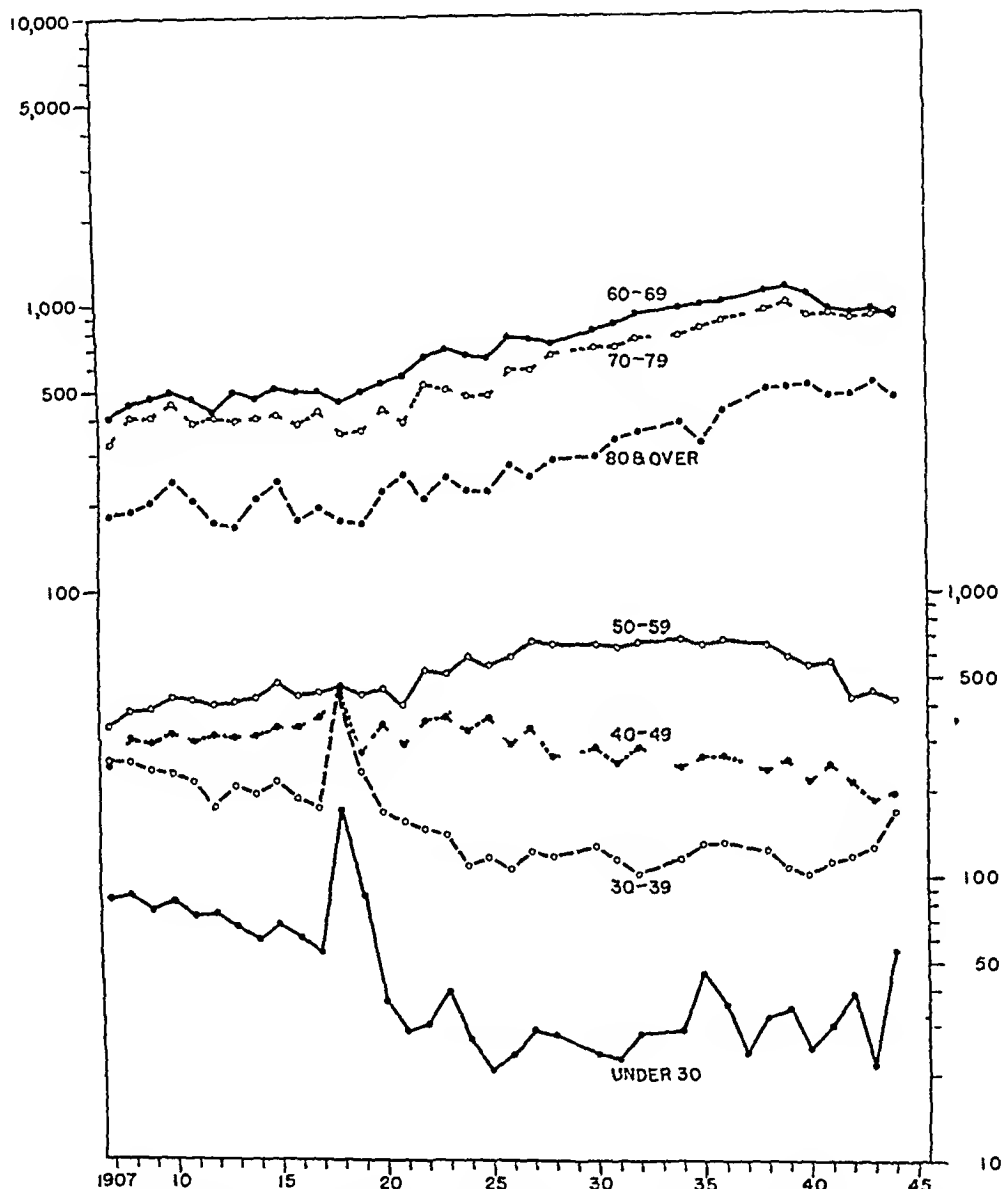
Last year a study was begun to determine the facts concerning the causes and rates of death among physicians in order that there may be shown a better

developing a process that should be of value to professional groups

It is impossible to state at present the exact time when these data will be available However, as soon as the work is completed an announcement of the details of publication and distribution of the data will be made

#### THE ANNUAL NUMBER OF DEATHS OF PHYSICIANS

At the outset a graph was plotted of the number of deaths of physicians reported year by year by *The Journal of the American Medical Association*



Deaths each year since 1907 among physicians by age groups (as reported by *The Journal of the American Medical Association*)

comparison of the death rates in the general population with those in the medical profession The Association will benefit in this study by the skill and experience of a well known statistician, Dr Louis I Dublin

Since this seems to be the first study of the kind for the determination of mortality rates for a professional group, much interest should develop in the results of the work, and since all the figures from this work will represent an original contribution as to both methods and rates, there should be considerable satisfaction in

tion since 1907 These data were broken down into age groups by decades, commencing with deaths occurring among physicians who were under 30 years of age The year 1907 was selected as the starting point, because the first edition of the "American Medical Directory" was then published and an accurate tabulation of the size of the medical population was henceforward possible

An unmistakable trend has developed which now has been maintained for more than thirty

<sup>9</sup> Report of Board of Trustees, J A M A 124 1262-1294 (April 29) 1944

years Year by year, fewer physicians under 60 years of age are dying, and more are living to attain 70 and 80 year marks It is of passing interest that the only demonstrable effect of the First World War on the curves was caused by the influenza epidemic The present war is unlikely to have any notable effect on the medical profession unless another pandemic of high virulence afflicts the world

The graph also suggests, by indirection, an aging medical population No record could be found of the age distribution of physicians in the United States at different periods, and therefore such a record was manufactured To tabulate by age groupings all the physicians listed in each edition of the "American Medical Directory" would have defied the energy of a behemoth To regard a single state as representative and to apply figures for that state from time to time to the medical population of the entire country

TABLE 1—*An Estimation of the Age Distribution of American Physicians\**

Physicians, Year Total	Under 40	40 to 49	50 to 59	60 and Over
1907 122,200	59,880 (49%)	30,550 (25%)	18,330 (15%)	13,440 (11%)
1921 145,400	50,890 (35%)	43,620 (30%)	27,630 (19%)	23,260 (16%)
1931 156,400	56,300 (36%)	35,970 (23%)	34,410 (22%)	29,720 (19%)
1942 180,500	77,000 (43%)	37,910 (21%)	27,080 (15%)	37,910 (21%)

\* In 1942, the Committee on Medical Preparedness of the American Medical Association estimated that at the beginning of the year there were 176,191 physicians in the continental United States Twenty four per cent were under 36 years of age, 22 per cent between 36 and 44, 18 per cent between 45 and 54 and 36 per cent 55 years of age and older (J A M A 119:650-653 [June 20] 1942) These figures suggest that the mode of reckoning used in assembling this table may have exaggerated the number of young physicians and underestimated the number who are older These miscalculations would make no difference in the conclusions drawn

seemed a reasonable way of meeting the situation and of acquiring sufficiently reliable information for the purposes of this paper Thus, the physicians of Massachusetts, as appearing in the directories for 1907, 1921, 1931 and 1942, were counted and were separated into age groups, and from these figures the age makeup of the American medical profession for these years was calculated

The figures support the premise that the average age of physicians at the time of death has been rising, together with an increasing percentage of all physicians living in the later decades of life It was between 1907 and 1921 that many of the weaker schools closed, and enrollments were low, and it was in 1918 to 1920 that many young physicians succumbed to influenza The influence of these factors is brought out by the relatively small number of physicians in 1921 who were less than 40 years old Ten years later, in 1931, and twenty years later, in 1942, as men of the relatively small classes and the survivors

of the influenza epidemic grew older, their low numbers were reflected in the makeup of the medical population as a whole Yet, in spite of this handicap, the total number of physicians living to pass the age of 60 has increased steadily

Since 1921, schools have enlarged and new schools have come into existence Presumably, therefore, in future, physicians of all age groups are likely to increase With the number of elderly men growing so steadily, the question must soon arise how best to utilize their talents and indeed how best to support them when they retire

#### THE CAUSES OF DEATH AMONG PHYSICIANS

The most common causes of death among physicians by ages at different periods were determined through an analysis of death notices in *The Journal* Various other observers have used this information Three especially entertaining investigations have been reported, resulting in three divergent conclusions—perhaps a salutary reminder to a novice in the statistical field of the difficulty of dealing with figures Rendich<sup>10</sup> attempted to discover whether medical prominence, as judged by length of a death notice in *The Journal*, was compatible with longevity and came to the conclusion that men who achieved sufficient fame for long obituaries were shorter lived than their less known colleagues Mills,<sup>11</sup> in contrast, disagreed with this and, using similar methods, thought he proved that the great were not inclined to die young and that their heritage was likely to be a ripe old age And Lehman<sup>12</sup> expressed the opinion that both were wrong<sup>1</sup>

For the purpose of this study the causes of death in a series of groups of 250 or more physicians of different ages occurring at about 1907, 1931 and 1942 were tabulated The year 1921 was omitted, because in that year the effects of the influenza epidemic were still evident and therefore death rates were atypical Deaths from battle injuries in the present war were also excluded The age groupings comprised physicians who died when they were less than 40 years old, 40 to 49, 50 to 59 and 60 years old and over It seemed desirable to assemble at least 250 cases in each of these age groups in order to have a reasonably large number from which to obtain a picture of the distribution of the common types of fatal illness at about the time under consideration, and in order to collect material of such size

10 Rendich, R A Average Age of Physicians at Death, Correspondence, J A M A 119 1041 (July 25) 1942

11 Mills, C A What Price Glory? Science 96 380-381 (Oct 23) 1942

12 Lehman, H C The Longevity of the Eminent, Science 98 270-273 (Sept 24) 1943

it was necessary to cull more than one year's yield. In scanning the reports from the early days, it was hard to find the cause of many fatalities among older men in any single year, whereas now it is difficult to find many fatalities among younger ones. Diagnoses were made as accurately as possible from the information presented—admittedly a matter of personal judgment since fashions in medical terminology have been fickle. In 1907 "acute indigestion" was often reported as a fatal illness, but no hesitancy is felt, through light of current knowledge, in including such cases among cardiac deaths. After the publication of Herrick's<sup>13</sup> paper, the diagnosis of coronary thrombosis began to appear and has flourished ever since. Epstein's<sup>14</sup> study of albumin and globulin ratios in edema commenced to make the diagnosis of nephritis less

pressed in percentage values of the causes of death for each series of groupings.

No attempt was made to analyze the cause of death of physicians over 60 years of age, for the diagnostic problems were almost invariably too complex. The appropriate classification of the cause of death of a physician over 70 years old reported to have succumbed to heart failure on an arteriosclerotic basis complicated by uremia from malignant disease of the bladder represents the type of riddle often encountered.

If one were interested solely in physicians who die, one would agree that vascular disease is now encountered very commonly as a cause of death among them at all ages and is increasing in frequency. Yet such a way of regarding the deaths of physicians is unsound, since no consideration is given to the number who are alive. In order

TABLE 2—The Common Causes of Death Among Physicians by Age Groups per Hundred Deaths in 1907, 1931 and 1942

	Under 40						40 to 49						50 to 59					
	1907 and		1931 and		1942 and		1907 and		1931 and		1942 and		1907 and		1931 and		1942 and	
	Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years		Surrounding Years	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Total number analyzed	493	100	290	100	356	100	382	100	230	100	332	100	467	100	531	100	353	100
Accidents	104	21	65	22	105	29	47	12	40	16	25	7	44	9	43	8	17	5
Pneumonia	72	15	45	16	27	8	46	12	36	15	19	6	45	10	38	7	16	4
Tuberculosis	62	12	29	10	12	3	17	5	10	4	11	3	14	3	12	2	6	2
Typhoid	49	10	0	0	0	0	12	3	0	0	0	0	7	1	1	0	1	0
Appendicitis	24	5	14	5	3	1	12	4	3	1	2	1	9	2	11	2	2	5
Other infections	37	8	46	16	24	7	23	6	21	8	7	2	22	5	24	4	2	5
Miscellaneous	68	14	37	13	77	22	89	23	40	16	86	26	93	20	114	19	60	17
Heart disease	46	9	39	13	73	20	69	18	73	29	145	44	115	25	248	43	198	56
Renal disease	22	4	9	3	15	4	43	11	7	3	11	3	53	11	20	3	6	2
Cerebral hemorrhage and thrombosis	9	2	6	2	20	6	24	6	20	8	26	8	65	14	70	12	45	13
All cardiovascular renal diseases	77	15	54	18	108	30	136	35	100	40	182	55	233	50	338	58	249	71

common, and Christian's<sup>15</sup> teaching of the importance of differentiating between cardiac and renal dropsy also played a part in increasing the number of reports of cardiac deaths at the expense of those previously reported as due to renal disease. Accidental deaths and deaths by suicide were grouped together as accidents, because in many instances it was difficult to ascertain whether a given death was self induced or was in fact due to misadventure. Cancer was regarded as a miscellaneous disorder, just as were rheumatic heart disease, cirrhosis of the liver, diabetes, the late effects of syphilis, postoperative deaths and the lymphomas or anemias, while subacute bacterial endocarditis was grouped with the unspecified infections. The results were ex-

to evaluate the data in a more comprehensive fashion and to give consideration to the numbers involved, an attempt was made to estimate what vital statisticians term specific death rates. According to Linder and Grove,<sup>16</sup> the specific death rate is a ratio the denominator of which represents the total number of deaths from any cause that could happen and the numerator the number that did happen. The specific death rate for each cause of death listed in table 2 and in each age group was obtained by the formula which they have advocated

$$m = \frac{d}{p}k,$$

where

$m$  = specific death rate for any defined cause

$d$  = deaths occurring to persons in a defined group from a defined cause within a stated time

$p$  = population in the defined group exposed to the risk of death from the defined cause within the stated time

$k$  = a constant—100,000 in the tables reported here

<sup>13</sup> Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59:2015-2020 (Dec. 7) 1912.

<sup>14</sup> Epstein, A. A. The Nature and Treatment of Chronic Parenchymatous Nephritis (Nephrosis), *J. A. M. A.* 69:444-447 (Aug. 11) 1917.

<sup>15</sup> Christian, H. A. The Mechanism of Edema, *J. A. M. A.* 97:296-299 (Aug. 1) 1931.

<sup>16</sup> Linder, F. E., and Grove, R. D. Vital Statistics Rates in the United States 1900-1940, United States Department of Commerce, Bureau of the Census, 1943.

In using this formula the number of deaths from any cause for any of the years or age groups considered was estimated by applying to the total deaths for the year and to the age group under consideration the percentage values of each of the causes of death that had been listed. The

TABLE 3—*Calculation of Specific Death Rate from Different Causes per Hundred Thousand Physicians Less Than Forty Years Old for Year 1907*

Cause	Number in Series	Per centage of Causes	Total Deaths for Year	Specific Death Rate per 100,000 for Each Cause Listed
Total cases	493	100	338	564
Accidents	104	21	71	119
Pneumonia	72	15	51	85
Tuberculosis	62	12	40	67
Typhoid	49	10	34	57
Appendicitis	24	5	17	28
Other infections	37	8	27	45
Miscellaneous	68	14	47	78
All cardiovascular renal diseases	77	15	51	85

There has been a satisfactory diminution in the relative number of deaths from all causes and among all ages, especially notable among those under 40 but perceptible among those over 60. This statement merely reiterates that, as fewer younger physicians die each year, it is inevitable there should be more deaths among those who are older.

Almost any historian, in glancing backward, would say that since 1907 the jugulation of typhoid fever, the suppression of tuberculosis and syphilis, improvements in preoperative and post-operative care, the development of new surgical technics and the discovery of chemotherapeutic agents like the sulfonamide drugs and penicillin are among the more conspicuous milestones. As each one has been passed, physicians as well as their patients have benefited.

In 1907, typhoid, next to pneumonia and tuberculosis, was the illness most often fatal to begin-

TABLE 4—*Common Causes of Death Among Physicians by Age Groups per Hundred Thousand in 1907, 1931 and 1942 (Specific Death Rate)*

Cause	Under 40			40 to 49			50 to 59			60 and Over		
	1907	1931	1942	1907	1931	1942	1907	1931	1942	1907	1931	1942
All causes	564	247	195	809	709	493	1,880	1,875	1,673	6,838	6,770	6,380
Accidents	119	55	57	98	114	34	169	151	85			
Pneumonia	85	39	15	98	106	29	191	181	66			
Tuberculosis	67	25	6	39	28	13	55	38	33			
Typhoid	57	0	0	23	0	0	16	0	0			
Appendicitis	23	12	1	33	8	5	37	38	9			
Other infections	45	39	14	49	56	10	92	76	9			
Miscellaneous	78	32	43	184	114	132	371	358	284			
Heart disease	50	32	39	148	205	215	480	800	939			
Renal disease	23	7	8	88	22	15	207	55	33			
Cerebral hemorrhage and thrombosis	12	5	12	49	56	40	262	228	215			
All cardiovascular renal diseases	85	44	59	285	283	270	949	1,083	1,187			

figures in table 1 were used for the population figures of the different groups.

As an example of the manner in which these problems in arithmetic were actually solved, consider the year 1907 and the deaths among physicians who were 40 years old and less. In that year and age group there were 59,880 physicians alive, of whom 338 died. By applying the percentage figures of the common causes of death of men in that age group at about that time to these 338 deaths, each was accounted for in a fashion designed to illustrate the average picture of the times, and thereafter population figures were applied according to Linder and Grove's formula.

This method of using the figures was employed throughout, and a tabulation was made by which the specific death rate from common causes among physicians at different ages and times were compared.

The table summarizes in diagrammatic form much of the progress of medicine for the last thirty-five years as it affects the profession

ning practitioners. Now there is no typhoid. Pneumonia, next to misadventure, was the most frequent cause of death to the young, and it caused older physicians as well to slip out of the world with great regularity. First came anti-pneumococcus serum and next sulfonamide compounds and penicillin, so that now this disease is much less threatening.

Relatively speaking, there are fewer fatal accidents than there were. Trains, bad roads, poor lighting and the horse and buggy actually were more dangerous to physicians than are automobiles and airplanes. Syphilis also probably played a part in making life hazardous. At least there were many more persons, both within and without the ranks of the medical profession, who were abnormally irascible, so that many more physicians were killed in those times than now, and there were a number of deaths from late syphilis, which now are no longer encountered.

The effect of advances in surgery is suggested by the figures for appendicitis. The treatment of

appendicitis has improved steadily, so that now this disease is of little danger to physicians. In 1907, or about that time, a number of deaths were reported concerning which no other information was given than that they followed an unspecified type of operation. At present, post-operative deaths from any cause are reported much less frequently.

Tuberculosis has been fought steadily. Among younger physicians, relatively, it is much less serious than it was, indicating at least that the careful search for it during the last few years which has been made among medical students has yielded results. Other infections, like cerebrospinal meningitis or erysipelas to mention two striking examples, have come under control recently. On the whole, it is plain that the lives of many physicians are now being saved each year which hitherto were lost.

The deaths from vascular disease are of particular interest. The specific death rates from

chosen because an overwhelming majority of physicians are white, are men and are above this age limit. Linder and Grove have divided the population into ages of 25 to 34, 35 to 44 and so on. Therefore, interpolations were adopted to make their age classification coincide with the one established here. The interpolations were as simple as possible to compare with the figures for physicians who were under 40, all of the figures for the 25 to 34 age group of Linder and Grove were used and one half of those of the 35 to 44 group, and to compare with those for the 40 to 49 age group of physicians, half of the figures in the 35 to 44 group and half of those in the 45 to 54 group of Linder and Grove were employed. Similar calculations were used in the 50 to 59 year group, and, finally, to compare with the figures for physicians 60 years old and over, half of those of Linder and Grove for 55 to 64 were used and all their figures for ensuing ages. This method, as Emerson<sup>17</sup> pointed out, is not

TABLE 5—*Death Rates from Certain Causes per Hundred Thousand Physicians in 1942 and in White Men More Than Twenty-Five Years Old in 1940 (Specific Death Rate)*

Cause	Under 40		40 to 49		50 to 59		60 and Over	
	Physicians	White Men	Physicians	White Men	Physicians	White Men	Physicians	White Men
All causes	195	535	493	723	1,673	1,830	6,390	5,800
Accidents	57	128	34	99	85	131		
Pneumonia	15	26	29	40	66	80		
Tuberculosis	6	70	13	71	33	93		
Heart disease	39	80	215	167	939	578		
Renal disease	8	20	15	42	33	117		
Cerebral hemorrhage and thrombosis	12	12	40	38	215	130		
All cardiovascular renal diseases	59	112	270	247	1,187	825		

renal disease and cerebral hemorrhage or thrombosis appear to be diminishing in each age group, while those from heart disease among physicians over 40 are increasing. Possibly the emasculation of certain acute infections has diminished the incidence of glomerulonephritis, though it seems more probable that this apparent trend is due to nothing more significant than variation in terminology. The basic pathologic factor in almost all the cases within these three groups is vascular disease. If they are considered as a single unit and as one disease, their specific death rate in the different age groups and at different times has remained remarkably constant.

Physicians differ little from the rest of the citizens of the United States in respect to the causes of their deaths at different ages. Linder and Grove have constructed a table giving the specific death rates of the country for eight leading causes in 1940, from which certain comparisons can be made with the figures of 1942 concerning physicians. In this comparison the figures for white men above the age of 25 from Linder and Grove were used. This group was

accurate, though the errors introduced probably do not affect the results.

The data in the table so constructed suggest that physicians up to the age of 60 are somewhat protected as a class, considerably fewer of them, for example, die of accidents and tuberculosis than of their controls, and their specific death rate from all causes is lower. On the other hand, their death rate from heart disease for persons over 40 is higher. This higher rate, however, is partially compensated for by their lessened liability to renal disease. Physicians past 50 appear to have proportionately more fatal cerebral vascular accidents than do members of the non-medical population and a slightly higher death rate from all causes than have men in other occupations. Emerson and Hughes<sup>18</sup> reported similar conclusions in 1926.

<sup>17</sup> Emerson, H. Personal communication to the author.

<sup>18</sup> Emerson, H., and Hughes, H. E. Death Rates of Male White Physicians in the United States by Age and Cause, *Am J Pub Health* 16 1088-1093 (Nov) 1926.

If, once again, deaths from heart disease, renal disease and cerebral vascular disease are grouped together, physicians between 40 and 60 years of age appear to die a little more commonly from these causes than do members of the general white male population, probably because they have a better chance of avoiding death from other insults. The differences at best are so slight as to be scarcely outside the limits of error entailed in the calculations.

In brief, there is nothing to prove that there has developed in the medical profession an ominous liability to coronary thrombosis or to any other manifestation of vascular disease. Nor has evidence yet developed to suggest that the danger to older physicians of overwork in wartime is much more than a bugbear. The viewpoint of Riesman and Harris and of Chadwick is sound. The increasing number of deaths among physicians each year from vascular disease is the price of medical advancement. So long as physicians continue to improve their methods and to build up a profession whose members grow

steadily older in years and larger in numbers, the mortality from vascular disease will increase.

Roger Lee<sup>19</sup> has written an essay which all physicians should read. Speaking of vascular disease in general, he said that at the moment there is no method or clue for lessening its mortality. He went on to suggest, as did Osler<sup>20</sup> before him, that worry rather than hard work is the more baneful influence in life. In order to pass old age as gracefully as possible, he advised his readers at all costs to maintain some sort of objective in life lest lacking this they literally curl up and die. When all is said and done, can any hard working practitioner, as an end to his career, ask for a fate more honorable than, like Phrontes in the *Odyssey*, to be struck suddenly by the gentle darts of Apollo and to be dropped dead with the steering oar of the moving ship within his hands?

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19 Lee, R. I. *Geriatrics: The Medical Care of the Elderly*, *New England J. Med.* **230** 190-193 (Feb. 17) 1944.

20 Osler, W. *Aequanimitas*, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1932.

# ABSENCE OF ELECTROCARDIOGRAPHIC CHANGES IN TSUTSUGAMUSHI FEVER (SCRUB TYPHUS)

REPORT OF TWO HUNDRED CONSECUTIVE CASES

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Observers of the tsutsugamushi fever (scrub typhus) which occurred in our Armed Forces early in the New Guinea Campaign, noted perivascular and interstitial infiltration of the myocardium with inflammatory cells plus changes in the muscle fibers of a varying degree<sup>1</sup> Weakness and tachycardia were not uncommon in soldiers convalescent from the more severe infections Because of these observations, the impression has been gained that residual cardiac damage might follow tsutsugamushi fever

TABLE 1—Time of Obtaining Electrocardiogram

	Number	Per Cent
During acute stage	10	5
1 to 4 weeks convalescent	184	92
6 to 12 months convalescent	6	3

The present study was undertaken to determine the possibility of electrocardiographic evidence of residual myocardial damage Tracings were obtained for 200 consecutive patients admitted to a station hospital between May 23 and Sept 1, 1944 Patients were seen at varying intervals following the onset of the disease It will be seen in table 1 that 184 (92 per cent) of the group were examined within one to four weeks after the acute symptoms had subsided Tracings were obtained for 10 patients during the height of the disease, while 6 others were examined six to twelve months after their illness All were men

Ninety per cent acquired their infection while in one of four of the highly endemic areas in New Guinea The distribution of these is seen in table 2

Of the recent convalescent group, 48 per cent showed evidence of eschars, 89 per cent still had some degree of adenopathy and all gave a history of a sustained febrile illness of seven to twenty-

four days' duration The blood serum of 50 per cent of the group still produced agglutination of *Bacillus proteus* Kingsbury strain in dilution of 1:160 or higher

## ELECTROCARDIOGRAPHIC OBSERVATIONS

In no instance was there an abnormal pattern which could be attributed to the disease The original tracing taken for 1 patient showed the diphasic T wave in lead I and inverted T waves in leads II, III and IV F A short QT interval caused a digitalis effect to be suspected<sup>2</sup> Investigation revealed that this man had received 14 cat units of digifolin intramuscularly ten days previously An electrocardiogram taken after a lapse of two weeks showed upright T waves in the limb leads, there was a shallow inversion of the T wave in lead IV and the QT interval had returned to normal<sup>3</sup>

Isolated deviations from the normal, based on the standards of the Criteria Committee of the New York Heart Association in 1939, occurred in 44 per cent of the patients This value is comparable to that observed by Viscidi and Geiger in their study of 486 adults between the ages of 18 and 38<sup>4</sup> In none of their cases was

TABLE 2—Area in Which Infection Was Acquired

Area	Per Cent
I	27
II	25.5
III	17.5
IV	17.5
Others	10

there a history of acute rheumatic fever or objective evidence of cardiac disease Using the same criteria, they found isolated deviations from

2 The value of K in Bassett's formula,

$$K = \frac{QT}{\sqrt{\text{cycle length}}}$$

was 0.342 as compared with the normal of 0.392

3 The value of K became 0.400

4 Viscidi, P C, and Geiger, A J Electrocardiographic Observations on Five Hundred Unselected Adults at Work, *Am Heart J* 26:763-768 (Dec) 1943

1 Corbett, A J Scrub Typhus, *Bull U S Army M Dept*, November 1943, no 70, pp 34-54 Lipman, B L, Byron, R A, and Casey, A V Clinical Survey of Scrub Typhus Fever, *ibid*, January 1944, no 72, pp 63-70

the normal in 488 per cent of their tracings. The incidence of the various types of isolated deviations from the normal occurring in their group as compared to this one is listed in table 3. It will be noted that they are in close agreement in most instances. Delayed auriculoventricular conduction was present four times (0.8 per cent)

TABLE 3—Incidence of Deviations

Limb Leads		Viscidi and Geiger's Series		This Series	
		No.	%	No.	%
P Wave					
Direction	Inverted in two leads	1	0.2	0	0
Amplitude	Largest P wave less than 0.5 or more than 2.5 mm			1	0.5
Duration	0.12 second or more	1	0.2	1	0.5
PR Interval					
	0.22 seconds or more	4	0.8	0	0
QRS Complex					
Duration	More than 0.10 second	2	0.4	0	0
Amplitude	Less than 5 mm in lead with largest amplitude or sum of over all dimension in the 3 leads less than 15 mm	9	1.8	5	2.5
Contour	Slurring in 2 or more leads	126	25.2	52	26.0
	Deep Q waves (exceeding 15%, 20% or 25% of largest QRS amplitude in leads I, II or III respectively)	8	1.6	0	0
Axis deviation	More than slight	5	1.0	0	0
RS-T Junction					
	Deviation from isoelectric level of more than $\pm 1$ mm	6	1.2	3	1.5
T Wave					
	Abnormal direction or amplitude	19	3.8	12	6
QT Duration					
	The value of K in formula $K = QT/\sqrt{\text{cycle length}}$ exceeds normal of 0.392	85	17	31	15.5
P Wave					
Direction	Inverted more than 0.5 mm	35	7	2	1
Amplitude	Greater than 1.5 mm	2	0.4	0	0
QRS Complex					
Amplitude	Over all dimension less than 8 mm	80	16	7	3.5
R Wave	Less than 3 mm	4	0.8	5	2.5
Q Wave	More than 3 mm	2	0.4	0	0
RS-T Junction					
	Deviation from isoelectric level or more than -0.6 mm or +2.0 mm	0	0	0	0
T Wave					
	Abnormal direction or amplitude	19	3.8	3	1.5

and delayed intraventricular conduction occurred twice (0.4 per cent) in their group, whereas neither occurred in this series. Deep Q waves occurred eight times (1.6 per cent) in their group but did not appear in this series. Abnormalities in the direction and amplitude of T waves was slightly less common in the limb

leads (3.8 per cent as against 6.0 per cent) but slightly more common in the precordial lead (3.8 per cent as against 1.5 per cent) in their group as compared to this series. (Inversion of the T wave occurred only once in the typhus group.) Low voltage of the QRS complex in the precordial lead was four and one-half times as common (16 per cent as against 3.5 per cent) in their series as in this one. There was a slightly greater incidence of low R waves in the group with tsutsugamushi disease (2.5 per cent as against 0.8 per cent), but this may be explained by the fact that all tracings were taken with subject in the supine position. In no instance was the R wave in lead IV less than  $\pm 1.0$  mm.

COMMENT

The absence of conduction disturbances and abnormal changes in the T waves in the electrocardiograms of this study is significant. A similar absence would not be expected after acute rheumatic fever or diphtheria, acute infections known to affect the heart muscle. Typhoid and other acute infections produce inflammatory changes in the myocardium similar to those seen in tsutsugamushi fever, without leaving demonstrable residual myocardial damage. Tachycardia which sometimes follows tsutsugamushi fever may well be vasomotor in origin, as it is in other prolonged febrile illnesses.

SUMMARY AND CONCLUSION

- 1 An electrocardiographic study was made of 200 consecutive patients convalescent from tsutsugamushi (scrub typhus) fever.
- 2 No abnormal electrocardiographic patterns were found.
- 3 The incidence of isolated deviations from the normal was no higher than that found in the electrocardiograms of healthy persons of the same age.

Lieutenant Colonel Philip W. Brown, Medical Corps, Army of the United States, gave help and criticism in this study, and Sergeant Stephen E. Fedorcha, Medical Department, Army of the United States, supplied technical assistance.

# SOUTH AMERICAN TRYPANOSOMIASIS (CHAGAS' DISEASE)

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The varied geographic areas in which American troops are stationed or operating in the present war are such as to expose them to a variety of diseases, some of which, though not rarities in the respective locales where infections may occur, are exotic if considered in the light of daily medical practice in the United States. Some of the diseases are of more serious consequence in the chronic stages than in the more acute periods and, unfortunately, more difficult to diagnose than. Many of the tropical protozoan diseases are of this character. It is a matter of no small consequence, therefore, that all physicians in the United States should have a wider knowledge of these and other tropical diseases than a mere acquaintance with their names. Clinical reports of the observations made by medical officers serving with American forces in the various theaters of operations will do much to acquaint American physicians with the more unusual diseases encountered among the troops and prepare the ground for more prompt recognition and treatment in the less obvious stages of development that may be encountered among some of them after return from foreign theaters. Needless to say, preventive measures to insure against spread of the diseases will also be more adequately anticipated and instituted.

It has been our privilege to make a diagnosis for, study and treat 2 American soldiers with South American trypanosomiasis, or Chagas' disease. Both were infected by the causative trypanosome in Panama, and both were observed during the acute stage of the disease. Although endemic cases of Chagas' disease have been recognized in nearly every American country from Mexico to Argentina, few reports and observations on the acute form of the disease in adults have been recorded in the American or English medical literature. From observations that have been previously made on the disease in Panama, it has been supposed that in this

area the disease, particularly in adults, is not clinically distinctive.<sup>1</sup>

In these 2 men, however, the acute stage of the disease was manifested by clinically distinctive symptoms, and in the second patient the disease picture was of the same type as has been observed in Brazil, Argentina and other South and Central American countries. Because of these facts and in order to call attention to the cardiac manifestations that may be exhibited during the acute and the chronic phases of the illness, we are presenting our observations on the 2 patients and also a brief summary of the more recent literature on Chagas' disease.

Chagas' disease, or South American trypanosomiasis, is essentially and primarily a disease of animals. It was first recognized and studied as such by Chagas in 1907. In 1909 he first recognized the disease in man. Many species of small mammals have been found to be naturally infected, and many others have proved experimentally to be capable of infection. Not only may the naturally infected mammals, such as the armadillo, opossum, rat and bat, serve as reservoirs for the spread and transmission of the disease, but domesticated animals, such as the dog, cat or guinea pig, may also become links in the transmission to man.<sup>1c, d</sup>

The etiologic agent is a protozoan parasite, *Trypanosoma cruzi*, which invades the blood and tissues of man or other mammalian hosts. It is transmitted from animal to man and from animal to animal through the medium of an insect vector of the genus *Triatoma*. The insect is infected only through the medium of infected blood from some mammalian host, *T. cruzi* is not transferred from insect to insect.<sup>2</sup> The lar-

1 (a) Johnson, C. M., and Kelser, R. A. The Incidence of Chagas' Disease in Panama as Determined by the Complement-Fixation Test, *Am J Trop Med* **17**, 385, 1937. (b) Johnson, C. M., and De Rivas, C. T. Six New Cases of Chagas' Disease in Panama with a Review of Previous Cases, *ibid* **16** 47, 1936. (c) Clark, H. C., and Dunn, L. H. Experimental Studies on Chagas' Disease in Panama, *ibid* **12** 49, 1932. (d) Johnson, C. M. American Trypanosomiasis, *M. Clin. North America* **27** 822, 1943.

2 Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, Philadelphia, The Blakiston Company, 1942, vol 1, pp 207-228.

Owing to lack of space, this paper has been abbreviated for publication in THE ARCHIVES by omission of a number of the illustrations. The complete article will appear in the authors' reprints.

val and nymphal forms may become infected and also serve as vectors. Experimental infections or at least harboring of the trypanosome has also been produced in other blood-sucking insects of the bedbug and tick families.<sup>3</sup>

Although the disease to date has been considered as one limited to South or Central American regions, it is to be remembered that it could become endemic in the United States. Naturally infected triatomas and ones capable of acting as vectors if infected have been found in the states of California, Texas, Arizona, New Mexico, Utah and Florida.<sup>4</sup> Johnson,<sup>1d</sup> however, has pointed out that only those triatomas which invade houses are of epidemiologic importance for the human disease. Clark<sup>1c</sup> has also pointed out that it is usually only as a consequence of man's moving in and disturbing the natural triatoma-mammal, parasite-host relationship that he becomes a victim of the infection.

Most authorities believe that the trypanosome enters the blood and tissues of its host from contamination of the wound at the feeding site or of a wound on a mucous membrane surface, such as the conjunctiva of the eye, by trypanosomes in the fecal material deposited nearby by the insect vectors.<sup>5</sup> Thus the *modus operandi* of transmission is similar to that by which epidemic typhus is transmitted to man by the louse rather than to that by which the malarial plasmodium is introduced by the female anopheles mosquito.

3 Strong<sup>2</sup> Johnson<sup>1d</sup>

4 (a) Kofoid, C. A., and Whitaker, B. C. Natural Infection of American Human Trypanosomiasis in Two Species of Cone-Nosed Bugs, *Triatoma Protracta* Uhler and *Triatoma Uhleri* Nerva, in the Western United States, *J. Parasitol.* **22** 259, 1939. Packchamian, A. Natural Infection of *Triatoma Gerslakeri* with *Trypanosoma Cruzi* in Texas, *Pub. Health Rep.* **54** 1547, 1939. Wood, F. D., and Wood, S. F. Present Knowledge of the Distribution of *Trypanosoma Cruzi* in Reservoir Animals and Vectors, *Am. J. Trop. Med.* **21** 335, 1941. Wood, S. F. Notes on the Distribution and Habits of Reduviid Vectors of Chagas' Disease in the Southwestern United States, *Pan. Pacific Entomologist* **17** 85, 1941. Wood, S. F. Observations on Vectors of Chagas' Disease in the United States. II. Arizona, *Am. J. Trop. Med.* **23** 315, 1943. Packchamian, A. Infectivity of the Texas Strain of *Trypanosoma Cruzi* to Man, *ibid.* **23** 309, 1943. (b) American Trypanosomiasis in Brazil, *Foreign Letters, J. A. M. A.* **121** 65 (Jan. 2) 1943.

5 (a) Brumpt, E. Mode de transmission de la maladie de C. Chagas, *Ann. de parasitol.* **17** 320, 1939. (b) Denecke, K., and von Haller, E. Recherches experimentales sur le mode de transmission et le cours de l'infection par *Trypanosoma cruzi* chez les souris, *ibid.* **17** 313, 1939. (c) Chagas, E. L'infection experimentale chez l'homme par *Schizotrypanum cruzi*, *Compt. rend. Soc. de biol.* **118** 280, 1935. (d) de Andrade, C. Chagas' Disease. Ocular Conjunctiva as Most Frequent Site of Infection, *Arch. Ophth.* **26** 341 (Sept.) 1941.

After a variable period in the blood stream, the trypanosome invades the parenchymal cells of some organ for which it has a predilection, in which it assumes the leishmanial form and multiplies by longitudinal splitting. Multiplication of the leishmanial form continues until the affected cells rupture and the parasites escape to reinvade the blood stream or other tissue cells.

The most frequent sites for invasion of tissue and proliferation by the parasites are the heart, brain and liver. The voluntary muscles, spleen, lymph nodes, adrenals, ovaries, testes, thyroid and skin have also been found to be invaded.

Johnson<sup>6</sup> has demonstrated that as long as the parasitized cells remain intact there is no cellular reaction. However, the rupture of the cell and the liberation of the parasites call forth an intense inflammatory reaction with infiltration of macrophages, lymphocytes and plasma cells in the interstitial and perivascular spaces. After the rupture of the affected cells, the lesion is healed by fibroblastic proliferation and scar tissue formation.

The clinical symptoms of Chagas' disease have been found to be varied, ranging from acute manifestations of the type associated with any severe febrile illness to symptoms so negligible as to pass unnoticed by the patient and even by the physician. Particularly has this lack of symptoms been noted in the disease as it has been previously observed among adults in Panama.<sup>1</sup> It is only during the acute stage of the disease that the clinical picture is diagnostic. In the chronic stages, the symptoms and signs exhibited are a reflection of the damage present in some organ, most often the heart.

In his earlier papers Chagas described in detail various forms of the disease, which he divided into five clinical types, namely, the pseudomyxedematous, the myxedematous, the cardiac, the nervous and the chronic form with subacute manifestations. He attributed these syndromes to involvement by the trypanosome of the heart and brain and of the thyroid, testes and other endocrine glands. In recent years, it has been conclusively demonstrated that such syndromes are not the result of infection with *T. cruzi* alone but are manifestations of other associated conditions, such as endemic goiter and cretinism which diseases are frequently observed in certain of the areas where Chagas made his original observations.<sup>7</sup>

6 Johnson, C. M. Cardiac Changes in Dogs Experimentally Infected with *Trypanosoma Cruzi*, *Am. J. Trop. Med.* **18** 197, 1938.

7 Lobo L., A. Doença de Chagas e bócio endêmico, *Brasil-med.* **53** 1031, 1939. Johnson<sup>1d</sup> Strong<sup>2</sup> Footnote 4 b.

In children and also at times in adults the infection is manifested as an acute febrile illness which varies considerably in severity, and in young persons it often terminates fatally. As a rule the younger the patient the more severe the symptoms. The incubation period is between seven and fourteen days being ten to twelve days in experimentally infected human beings.<sup>8</sup> The fever may last from a few days to several weeks with the temperature ranging to 104 F or higher. There does not appear to be any specific type of temperature curve but the fever is usually remittent or intermittent in type.<sup>9</sup>

A common early sign of the disease, sufficiently characteristic to be of diagnostic value, is the unilateral (occasionally bilateral) trypanosomal ophthalmia which has been designated Romana's sign. The swelling of the lids starts abruptly extends outward to involve the neighboring tissue of the face and tends to disappear slowly. Painless edema, a reddish violet discoloration of the lids with conjunctival injection and occasionally, chemosis are present. The cornea is not affected and conjunctival secretion is scanty. The preauricular parotid submaxillary or cervical lymph nodes on the same side are frequently enlarged. Clinical cases often are characterized by this stubborn unilateral ophthalmia which persists throughout the acute febrile stage of the disease. It is believed that the inflamed eye marks the site of inoculation of the infected material from the reduvius vector.<sup>10</sup> Experimentally it has been shown that human beings and animals can be infected by having the excreta of infected bugs placed on the conjunctiva.<sup>11</sup>

In cases of severe infection an extensive edema, involving not only the face but the extremities and even the whole body has been described. It is said to be a hard edema of elastic consistency, which does not pit on pressure. Chagas believed that the edema was due to a myxedematous infiltration of the subcutaneous tissues resulting from the specific action of the parasite and its toxin on the thyroid gland, a view which is no longer tenable.<sup>12</sup> Transient edemas character-

istic of the early stages of African trypanosomiasis are assumed to be due to a general toxic action of the parasite and it is probable that the edema of the acute stage of Chagas' disease is a closely related phenomenon. There is little doubt that the edema observed in the chronic stage marked by severe myocardial damage is simply a result of cardiac decompensation.

In some cases the clinical signs and symptoms of meningoencephalitis are the predominating observations. These cases are almost uniformly fatal. The brain and meninges, when involved, are congested and edematous, with numerous small inflammatory foci scattered throughout the brain substance. On section, these lesions are found to consist of collections of neuroglia and mononuclear cells. These foci are not related to the blood vessels and occur in all parts of the brain. Parasites may be found in the spinal fluid in the neuroglia and in the large mononuclear cells of these inflammatory foci.

Because of the apparent predilection of *T. cruzi* for the myocardium, cardiac symptoms are frequent accompaniments of the disease. In general the cardiac manifestations of the acute stage are ill defined and may be indicated solely by the distant quality of the heart sounds, tachycardia and definitely irregular rate and rhythm. The acute stage lasts from four to eight weeks, and, in those patients who survive, the temperature returns to normal, trypanosomes disappear from the blood, and the edema and other signs of disease disappear. Occasionally the acute stage is prolonged for months. E. Chagas<sup>13</sup> stated the belief that in the absence of reinfection the disease may die out, while C. Chagas and others have stated that spontaneous cure does not occur and that those who escape death go on into the chronic stage of the disease.<sup>14</sup>

At death, in the acute stage of the disease, the heart is usually found to be enlarged and often shows a yellowish mottling of the myocardium. Occasionally the pericardial sac contains an excess of fluid of a greenish or yellowish green color sometimes containing a few fibrinous flakes. According to Chagas, cardiac enlargement is due primarily to dilatation, with little or no myocardial hypertrophy.<sup>15</sup> Microscopically, an intense myocarditis with parenchymatous degeneration and an associated infiltration of the interstitial tissues by lymphocytes plasma cells, round cells and macrophages is observed. The muscle fibers are widely sepa-

8 Strong<sup>2</sup> Chagas<sup>5c</sup>

9 Mazza, S, and others. Investigaciones sobre la enfermedad de Chagas, Publication 43, Universidad de Buenos Aires, Mision de estudios de patologia regional argentina, Buenos Aires, Universidad de Buenos Aires, 1940, Publications 46 and 51-53. Johnson<sup>1d</sup> Strong<sup>2</sup>

10 Chagas, E. and Dias, E. Romana Sign, Hospital Rio de Janeiro 19.185, 1941

11 Johnson<sup>1d</sup> Footnote 5

12 Yorke, W. Chagas Disease. A Critical Review, Trop Dis Bull 34 275, 1937. Johnson<sup>1d</sup> Strong<sup>2</sup> Footnote 4b

13 Chagas, E. Summula dos conhecimentos actuaes sobre a Trypanosomiose Americana, Mem Inst Oswaldo Cruz 30.387, 1935

14 Johnson<sup>1d</sup> Strong<sup>2</sup> Yorke<sup>12</sup>

15 Chagas, C. A forma cardiaca da Trypanosomiose Americana, Arch brasil de med 18.46, 1929

ated from one another, and some show fragmentation and hyaline degeneration. Large nests of the leishmanial form of the parasites may be found either in the muscle fibers themselves or in large mononuclear cells lying between the muscle fibers. If the parasitized fibers remain intact, there is no cellular reaction around them or edematous separation. It is only after rupture and liberation of the parasites that the characteristic intense inflammatory reaction occurs.<sup>6</sup> The epicardium and endocardium likewise often show signs of cellular infiltration and of nests of parasites.

If the disease progresses, cardiac symptoms become more manifest. The patient may complain of easy fatigability, palpitation, faintness, vertigo, exertional dyspnea, vague precordial pains and a sense of constriction in the chest. Occasional radiation of pain to the neck has been described. The more common physical signs are cardiac enlargement, edema, fall of blood pressure and cardiac arrhythmias. Clinical and roentgenologic examination may reveal cardiac enlargement usually involving both ventricles but especially the left. This enlargement may progress with the disease and reach the degree of a *cor bovinum*.

The changes that occur in cases characterized by chronic cardiac disturbances are less well known. E. Chagas stated<sup>13</sup> that the chronic form of the disease reveals hyperplasia of the connective tissue, with fibrosis and parenchymatous degeneration. He stated that the parasites tend to migrate to neighboring regions, so that, adjacent to fibrotic areas, acute lesions characterized by inflammatory cellular exudate, degenerative muscle fibers and occasional parasitized cells are to be found.

Arrhythmias constitute a most important feature of the cardiac picture. These have been attributed to the localization of the parasite in the musculature of the heart which either interferes with the conductivity or increases the excitability of the muscle.

The most intensive pathologic changes in the heart have been found in experimental animals to be in the cardiac muscle adjacent to the epicardium and endocardium, particularly severe at the base of the heart and near the auriculoventricular junction.<sup>6</sup> Chagas and Villela<sup>16</sup> have described the following cardiac arrhythmias: sinus tachycardia and bradycardia, premature systoles of ventricular, auricular and nodal origin, all stages of auriculoventricular block from prolonged auriculoventricular conduction

to complete auriculoventricular block, auricular fibrillation and flutter, paroxysmal tachycardia and alternans of the heart. Changes in rhythm may occur from day to day. The associated clinical manifestations do not differ from those associated with other cardiopathies. Low voltage of the QRS complexes and flattening of the P and T waves have also been described. With cardiac decompensation the symptoms and signs of pulmonary and systemic engorgement occur. The prognosis of the cardiac form of the disease is poor. Sudden death is common, especially in cases of heart block and ventricular arrhythmias. E. Chagas<sup>17</sup> reported a sudden fatal outcome in 27 out of 35 cases of Chagas' disease.

The frequency of occurrence of chronic myocardial disease in areas where human infection with *T. cruzi* is known to occur has led Yorke and others to believe that South American trypanosomiasis is responsible for many of these cases.<sup>18</sup> Some think the chronic cardiac form of the disease to be a sequel of acute infection in childhood, others, that it is a consequence of repeated infection in later life.<sup>19</sup>

The appearance of cutaneous eruptions as a manifestation of the acute stage of the disease has not been generally appreciated until recent years. Clark first reported this as a manifestation of the disease in 1932,<sup>10</sup> but his observation appears to have gone by unappreciated until clinical and pathologic descriptions of cutaneous lesions were called attention to by Mazza and his collaborators in 1940.<sup>9</sup> Mazza has classified the lesions into two large groups: first, "chagomas" and, second, "schizotrypanomides." The latter he considers true exanthems.<sup>9</sup>

The first is a nodular and/or ulcerative granulomatous type of lesion occurring at the primary site of invasion by the parasite. The histopathologic description is similar to that of any granulomatous process with tuberculoid formation, with giant cells similar to the Langhans type and with lymphocytic and mononuclear infiltration. The one distinguishing feature is the demonstration of the leishmanial forms of the parasites in the large mononuclear cells found abundantly in the subepidermal layers and

17 Chagas, E. Estudio electro-cardiográfico na forma cardíaca da Trypanosomíase americana, *Folha med* 2 97, 1930.

18 (a) Mazza, S., Basso, R., and Jong, M. E. Investigaciones sobre la enfermedad de Chagas. I. Primer caso mortal de forma crónica cardíaca de enfermedad de Chagas, comprobado en Mendoza, Publication 42, Universidad de Buenos Aires, Misión de estudios de patología regional argentina, Buenos Aires, Universidad de Buenos Aires, 1939, p. 3. (b) Johnson<sup>14</sup> Strong.<sup>2</sup> Footnote 4 b Mazza and others.<sup>9</sup> Yorke.<sup>12</sup>

19 Footnote 4 b Yorke.<sup>12</sup> Mazza, Basso and Jong.<sup>18a</sup>

16 Chagas, C., and Villela, E. Forma cardíaca da Trypanosomíase americana, *Mem Inst Oswaldo Cruz* 14 5, 1922.

about the lymphatic spaces. He describes these lesions as arising at the primary site of inoculation ("chagomas of inoculation") and also as occurring during the course of the disease at other cutaneous sites ("chagomas due to hematogenous spread"). In reading the clinical and histopathologic description of the "chagomas" recorded by Mazza, we were particularly impressed by the similarity between these lesions and the ones we have observed in cases of South American cutaneous leishmaniasis. Mazza particularly stressed the great similarity between the "chagomas" and the granulomatous lesions of sporotrichosis. Johnson<sup>20</sup> has also noted the similarity between cutaneous South American leishmaniasis and sporotrichosis and in 1939 made a brief mention of it. This similarity is a point of some significance in differential diagnosis and one not widely appreciated as yet in articles or textbooks dealing with these diseases.

The cutaneous lesions of the second group are histologically indistinguishable from the common exanthems, such as roseola or rubella. Mazza<sup>9</sup> expressed the opinion that much of the inflammatory reaction seen in these lesions is due to an explosive type of local tissue allergy, which is set off by the lodgment of a few of the parasites in a skin that for some reason has become sensitized to the organism. It is a type of reaction much like that seen in some of the other "ids."

The "schizotrypanomides" occur only after the disease has become systemic. Three clinical types have been observed: the morbilliform, the urticarial and the erythematous maculopapular eruptions.

The morbilliform type of reaction strongly resembles that of roseola or rubella and appears on or about the fifteenth day of the illness, usually after Romãña's sign has become fully developed. Urticarial lesions have also been observed at about this time. The third type, which is described as comprising multiple, discrete maculopapular erythematous blanching eruptions of varying size, appears between the fifth and twenty-fourth day of the disease, usually on the anterior surface of the chest, upper part of the abdomen or extensor surfaces of the arms and thighs. The face, palms, soles and mucous membranes are not involved.

Hepatomegaly is often observed. On pathologic study, the organ reveals parenchymatous changes with fatty degeneration. The presence

of the parasite in the parenchymal cells and Kupffer cells has been recognized.

The spleen may be somewhat enlarged and appears congested. The preauricular and cervical lymph nodes are often enlarged, and histologic examination reveals congestion, lymphoid hyperplasia, mononuclear cell production and phagocytosis.

Other symptoms which may be encountered from time to time depend on the visceral site of invasion by the parasite. Thus, myalgic pain, testicular pain or swelling and adrenal insufficiency are among those that have been reported.

Histologic changes of the general character previously described have been observed in the thyroid, adrenals, ovaries and testes of patients who died in the acute stages of the disease.

The changes that occur in the skeletal muscles are essentially similar to those that occur in the heart. Between the muscle fibers are small foci of cellular infiltration, and parasites may be found both within the muscle fibers and in large mononuclear cells lying between them.

Often the symptoms and physical signs just outlined are so clearcut and distinctive as to justify a clinical diagnosis of Chagas' disease on these grounds alone. In other instances laboratory proof will be necessary. In all instances laboratory confirmation should be sought.

Confirmatory diagnosis of the disease is directed toward either actually demonstrating the parasite or obtaining satisfactory evidence of its presence in the host by serologic methods. In the acute stages, the simple microscopic examination of fresh cover slip preparations or of stained thick blood films may suffice to disclose the presence of the trypanosome. Thick drop preparations of blood are usually necessary because of the scarcity of parasites circulating in the peripheral blood. When the parasites are too scanty to be detected in this way, inoculation of 5 to 10 cc of the suspected blood into guinea pigs or puppies and examination of the blood after two weeks may allow one to demonstrate the parasite. Killing the animals after a few more weeks often permits one to demonstrate the parasite in the cardiac muscles or other tissues on histologic examination. Another method of demonstrating *T. cruzi* in the peripheral blood is that to which Brumpt<sup>21</sup> gave the name "xenodiagnosis." It consists in allowing laboratory-bred, known uninfected triatomines to feed on the patient suspected of having the disease and in ascertaining after about two weeks

20 (a) Johnson, C. M. Personal communication to the authors. (b) Clark, H. C. Annual Report of the Gorgas Memorial Laboratory, 1939, House Document no. 543, 76th Congress, 3rd Session, Washington, D. C., Government Printing Office, 1940, p. 11.

21 Brumpt, E. Le xenodiagnostic. Application au diagnostic de quelques infections parasitaires et particulier a la trypanosomose de Chagas, Bull. Soc. path. exot. 7:706, 1914.

whether the intestinal tract of the insect contains the parasites

A more efficient test for the presence of Chagas' disease is the complement fixation test of Guerreiro and Machado<sup>22</sup>. These investigators found a glycerin and water extract of the heart and spleen of heavily infected puppies to be a highly specific antigen. In 1936, Kelser<sup>23</sup> described a modification of this test in which artificial cultures of *T. cruzi* were used as an antigen. Romana and Dias<sup>24</sup> have recently reported a further modification of the test. They used an alcoholic antigen of the cultured forms instead of the glycerin-saline solution antigen of Kelser.

goencephalitis, on biopsy of infected muscle and in cutaneous lesions. Other nonspecific laboratory observations which have been stressed by Mazza<sup>9</sup> are the pronounced degree of lymphocytosis which persists throughout the acute stage of the disease and the increase of eosinophils toward the latter part of the acute illness.

A progressive hypochromic anemia has been noted in some instances, particularly among children.

#### REPORT OF CASES

CASE 1—A white American soldier, aged 29, was admitted to an army station hospital in Panama on Dec 15, 1942, for observation for possible intracranial injury after a fight with another soldier. Except for

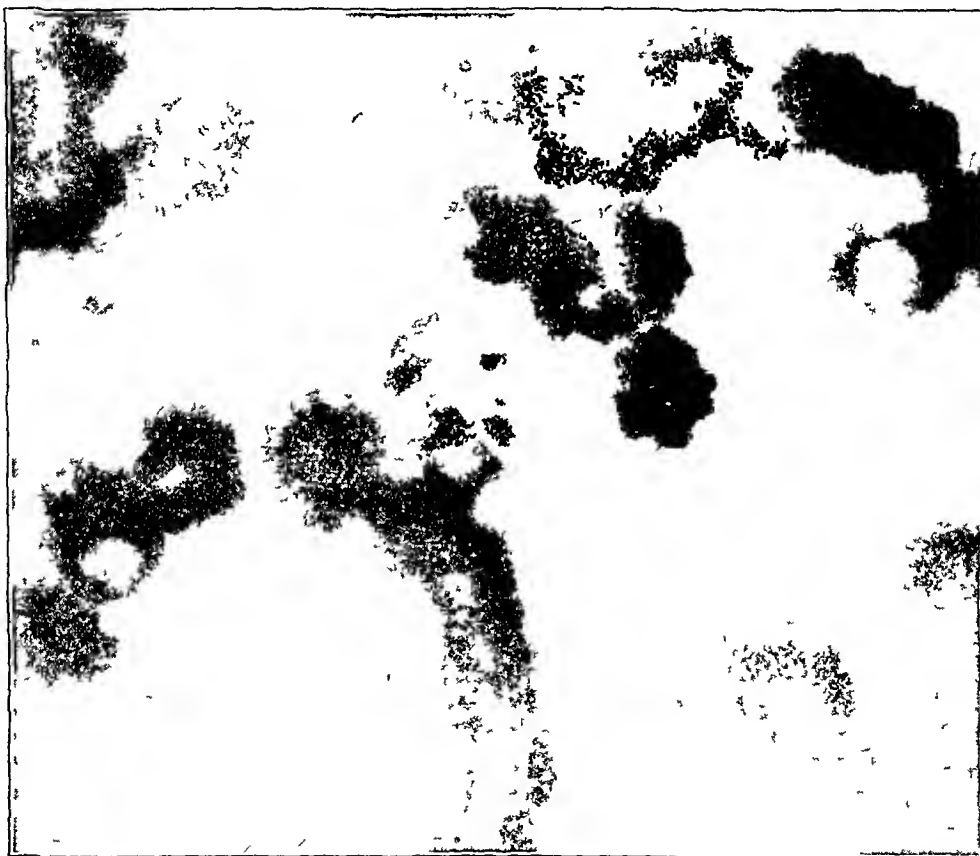


Fig 2 (case 1)—Photomicrograph of *T. cruzi* as identified in thin blood smear. Note the characteristic C-shaped form in which the parasite appears. The nucleus is in the central portion. The large oval kinetoplast is situated posteriorly. At this magnification the kinetoplast is seen to consist of two bodies. The larger, more proximally placed, body is the parabasal body. The smaller body, situated in the posterior end of the parasite, from which the flagellum arises is the blepharoplast. These are the distinguishing identifying features of *T. cruzi* in its trypomastigote form, as found in the circulating blood.

*T. cruzi* has in some instances been demonstrated in the spinal fluid of patients with menin-

22 Guerreiro, C, and Machado, A. Da reaccao de Bordet e Gengou no molestia de Carlos Chagas como elemento diagnostico, *Brasil-med* 27 225, 1913.

23 Kelser, R. A. A Complement-Fixation Test for Chagas Disease Employing an Artificial Culture Antigen, *Am J Trop Med* 16 405, 1936.

24 Romana, C, and Dias, E. Recao de fixacao do complemento na Doenca de Chagas, com antigeno alcoolico de cultura do "*Schizotrypanum cruzi*," *Mem Inst Oswaldo Cruz* 37 1, 1942.

a mild headache, he was symptom free at the time of admission. He had been stationed at various posts on both the Atlantic and Pacific sides of the Isthmus in the preceding two months and had been assigned to a recently cleared jungle position for a week prior to his admission to the hospital. He gave no history of any recent insect bites. Except for an attack of malaria in May 1942 and acute gonorrhea in September 1942, his general health had been excellent. His past history was otherwise not contributory.

Examination on his entry revealed a well developed and well nourished man who did not appear acutely ill. The temperature was 99.5 F and the pulse rate 100.

per minute. A mild seborrhea of the scalp and face, several superficial abrasions about the face and some mildly contused areas on the trunk were noted. The eyes, ears, nose and throat were essentially normal. The thyroid gland was not palpably enlarged at the time of the initial or subsequent examinations. The lungs were found to be clear on percussion and auscultation. The heart was not enlarged, and the rhythm was regular. A soft systolic murmur was heard over the apex. The blood pressure was 100 mm of mercury systolic and 70 mm diastolic. On abdominal examination, the tip of the spleen could be felt below the left costal margin. It was firm and nontender.

*Course in Hospital*—On the fifth day in the hospital, the patient had a chill, with a subsequent rise of temperature to 104.5 F. Physical examination at that time revealed nothing abnormal except the previously mentioned palpable spleen. A blood smear was positive for *Plasmodium vivax* on this day, and quinine therapy was started. The therapeutic response was prompt. Two days later, he began to complain of generalized muscular aching and severe pain in the knee joints and in the fingers of both hands. There was no clinical evidence

that the leishmanial form of the parasite is the one that produces the damage, it was felt that an antimony preparation should, at least theoretically, prove of some benefit. On Jan 10, 1943, his twenty-seventh day in the hospital, administration of an antimony preparation was started, 3 cc of fuadin was given intramuscularly. As to whether the drug was of any specific benefit to the patient or not is speculative, but improvement was promptly noted, and his fever began to subside. He received 13 cc of fuadin intramuscularly during the next ten days, and, in all, 33 cc was given over a period of forty-seven days. All of his symptoms disappeared during this period, and he made an uneventful recovery. He at no time showed evidence of cardiac damage and was discharged to full duty status on his ninety-fourth day in the hospital.

Clinical laboratory studies showed the patient to have a moderate anemia of a hypochromic type, which responded satisfactorily to iron and dietary measures. He was also observed to have a lymphocytosis and an elevated sedimentation rate. The significant hematologic findings we have summarized in table 1. The reaction to a complement fixation test (Johnson and

TABLE 1—Results of Hematologic Examinations (Case 1)

Date	Red Blood Cells	Hemo- globin	White Blood Cells	Poly- morpho- nuclear Leuko- cytes	Lympho- cytes	Eosino- phils	Mono- nuclear Leuko- cytes	Blood Sedimen- tation Rate, Mm	Comment *
December 19		80	5,650						Smear positive for <i>Plasmodium vivax</i> .
December 28	3,400,000	74	11,250	77	21	2		96	Smear negative for <i>P. vivax</i> .
December 30	3,050,000	80	5,500	68	30	2			Smear negative for <i>P. vivax</i> .
January 3									Icterus index 10, smear positive for <i>Trypanosoma cruzi</i> .
January 9	3,800,000	83	8,300	68	25	4		89	Platelet count 365,000, bleeding time 4½ minutes, clotting time 3¾ minutes.
January 14	3,500,000	80	6,350	68	30	2			Total protein 7.7 Gm.
January 21	4,450,000	80	8,000	66	33	1			
January 29			5,400	49	43	8		52	
February 7								24	
February 14			5,650	35	62	2	1	15	
February 22			5,400	59	41				
March 1	4,510,000	85							
March 8		90	4,700	44	49	6	1		

\* The reactions to the Takata-Ara and Napier's serum tests were negative, and the total serum protein was not increased.

of an inflammatory reaction in any of the joints at this time. In spite of adequate doses of quinine sulfate and quinacrine hydrochloride, the patient continued to have a daily remittent fever. Several cultures of the blood showed no growth, and repeated malaria smears were now negative for causative organisms.

On the twelfth day in the hospital an area of redness was noted about the nose and malar eminences. The next day, the right malar eminence appeared swollen. This area was not tender and did not pit on pressure. It gave a sensation to the palpating finger of firm induration of the subcutaneous tissues. The posterior cervical lymph nodes were moderately enlarged bilaterally. The inflammatory hyperemia subsided with the local use of hot compresses and the oral administration of sulfathiazole, but the fever and swelling persisted. This induration gradually subsided during the next three weeks. On the eighteenth hospital day, three days after administration of sulfathiazole had been discontinued, the proximal interphalangeal joint of the left middle finger became red, hot, swollen and tender. At this time, Capt. James R. Schmidt, the hospital pathologist, reported the presence of *T. cruzi* in one of the blood films (fig. 2).

In view of the lack of any recognized specific therapy for this disease and because of the pathologic evidence

Kelser modifications of the Guerrero and Machado test), performed for us by Dr. Johnson, of the Gorgas Memorial Laboratory, was reported as negative.

Roentgenograms revealed clear pulmonary fields and a normal cardiac silhouette.

An electrocardiogram taken January 11 revealed a sinus mechanism with a rate of 93 per minute and a conduction time of 0.16 second. The QRS complexes measured 0.08 second. The T waves were upright and normal in all the leads. A second electrocardiogram taken on March 2 was likewise normal.

**CASE 2**—A white American soldier, aged 27, was admitted to an army station hospital in Panama on Oct. 18, 1943, with the chief complaint of a swollen right eye of seven days' duration. He had been on duty in Panama for the past twenty-four months, and his only previous illness had been an attack of malarial fever in May 1942. He dated the onset of his present illness to one week prior to his admission to the hospital, when he began to notice progressive painless swelling of the right eye. Forty-eight hours before his admission, he experienced mild generalized malaise and fever but no chills, sweats or headache. The eye, though extremely swollen at that time, was not painful, nor was there an excessive secretion of tears or any discharge. There were no symptoms referable to the cardiac, respiratory, gastro-

intestinal or genitourinary systems. Local medication applied at his battalion aid station produced no beneficial effects on the ocular edema, and with the development of fever and malaise he was sent to the hospital. On further subsequent questioning, the additional history was elicited from the patient that in the vicinity of the hutment in which he had been quartered there were many "cone-nosed bugs." He had observed these insects on many occasions attempting to gain entrance into the screened enclosure at night, and on several occasions he had crushed these insects when they were clinging to his clothing and had noticed that they gave evidence of previous blood meals. He also remembered that between two and three weeks previously he and several of his companions had captured a sloth on which "cone-nosed" insects were feeding. He had no recollection of any insect bites.

Examination shortly after his admission to the hospital revealed an alert, cooperative, well developed and well nourished man who did not appear acutely ill. The temperature was 101 F and the pulse rate 100 per minute. The right eye was almost completely closed



Fig 3 (case 2)—Romana's sign. This photograph was taken during the fourth week of the illness, and much of the palpebral edema had subsided by this time. Enough edema remains, however, to illustrate the type of swelling and its distribution.

by edema of both the upper and the lower lids (fig 3). The edema extended outward to involve the soft tissues of the right malar eminence. The overlying skin revealed a pinkish discoloration. The area was not painful and did not pit on pressure. Though firm in consistency, the tissues were elastic and without evidence of subcutaneous infiltration. The conjunctival surfaces were hyperemic, with scanty secretion. The right preauricular lymph node was enlarged, firm and slightly tender. Scattered over the anterior thoracic wall, shoulders, upper arms, forearms, abdomen and back were discrete, circumscribed macular blanching erythematous plaques, varying in size roughly from that of a 25 cent coin to that of a silver dollar. Some of the lesions did not blanch completely on pressure and felt infiltrated but were not elevated. A few showed confluence, but the majority were distinct and separate. These lesions were asymptomatic, and the patient had not noticed them. At no time were they painful or pruritic. The thyroid gland was not found

to be enlarged on initial or subsequent examinations. The lungs were observed to be clear on percussion and auscultation. Percussion revealed no cardiac enlargement, and no murmurs or arrhythmias were noted. The blood pressure was 130 mm of mercury systolic and 68 mm diastolic. The remainder of the physical examination revealed nothing abnormal.

*Course in Hospital*—On the basis of the history and physical observations, a clinical diagnosis of Chagas' disease was made. It was not until the twenty-sixth day of his illness, however, that the clinical diagnosis was confirmed by laboratory evidence. On that day his complement fixation reaction was found to be strongly positive. One tested previously during the first week of his illness had been reported as negative. On the thirty-first day of his illness additional laboratory proof was evidenced when *T. cruzi* was demonstrated in the blood and tissues of 1 of the guinea pigs that had been inoculated with the patient's blood during the first week of his illness. Repeated attempts during this time to demonstrate the parasite in thick and thin blood films were unsuccessful.

During the first two weeks of his illness the patient had a daily temperature varying between 99 and 103 F and showed signs of increasing debility. Because of the apparently beneficial results from antimony observed in case 1, treatment with fuadin was started on the eleventh day of his illness, it being decided that his clinical course was such that a further wait for laboratory confirmation would not be justified. He received the drug by intramuscular injection at spaced intervals during the next eight weeks, a total of 83 cc of the drug was administered in two courses, with a two week interval during which none was administered. There was a gradual fall in temperature during the first two weeks of drug therapy, when the temperature varied between 99 and 101.5 F. Thereafter he had a slight daily elevation of temperature until December 18. During this period, the cutaneous rash faded and had completely disappeared by the seventeenth day in the hospital. No desquamation, scarring or recurrence of the rash was observed. The edema of the eye gradually subsided during the first seven weeks, although a residual discoloration of the lids persisted for several weeks afterward. The enlarged preauricular lymph node decreased in size from the thirty-second to the sixtieth day, when it could no longer be palpated. In addition to the previously described enlargement of a lymph node, during the second week of his illness a shotty lymphadenopathy of the posterior chain of cervical lymph nodes developed. These persisted until the fortieth day of his illness. Testicular pain was complained of during the third and fourth week of his illness. No swelling of either testis or epididymis was observed.

Early in the course of his illness, despite various apparent improvements, including the lowering of his temperature, decrease in the ocular edema and clearing of his cutaneous eruption, it became apparent that the patient was suffering cardiac damage. During the third week of his illness the slightest exertion resulted in prolonged tachycardia, and during the fourth week of his illness tachycardia at absolute rest became apparent. A soft apical systolic murmur became manifest at this time, along with frequent runs of ventricular extrasystoles and a diastolic gallop rhythm. The last was associated with electrocardiographic evidence of a prolonged PR interval. The rhythm changed frequently, and dropped beats were evident. The heart sounds were of poor tonal quality, suggesting a flabby myocardium. By percussion the left cardiac border was interpreted as being increased, as compared with the size determined

on his admission to the hospital. Confirmatory roentgenographic evidence of left ventricular enlargement was also obtained at this time. Additional evidence of myocardial damage was found in the changes observed in the serial electrocardiograms that were taken. During the early stage of the disease these revealed pronounced inversion of the T waves consistent with serious myocardial damage.

Although pericardial effusion has been reported in cases of Chagas' disease,<sup>25</sup> it is not common, and it is our opinion that the electrocardiographic and roentgenographic findings represented changes due to diffuse myocardial damage with cardiac dilatation rather than incident to an undetected pericardial effusion. With return of the cardiac silhouette to normal, the T waves became upright, but the electrocardiographic tracings continued to show evidence of a severe conduction disturbance between the auricle and ventricles. Thus it is evident that, in addition to diffuse myocarditis, focal lesions in the conducting system also occurred.

From the fourth to the eighteenth week of the patient's illness it was daily noted that his pulse and cardiac rate and rhythm were subject to wide and frequent variations. An explanation for this changing rate and rhythm

illness. The pathologic changes which occurred in the auriculoventricular conducting pathway are apparently of a permanent nature, since little or no improvement of the heart block was noted during the period of over five months that he was under observation.

**Laboratory Studies**—Repeated blood counts revealed essentially normal values for hemoglobin and red blood cells. On November 5, the white blood cell count rose to 13,300, with a definite increase in the lymphocytes (table 2). For several days prior to this, during examinations of blood films for trypanosomes, atypical lymphocytes of the type seen in infectious mononucleosis were observed. The heterophile antibody reaction was positive at this time. Later, this reaction became negative. A significant degree of lymphocytosis was present throughout most of the patient's stay in the hospital, a period of over five months.

These hematologic observations are presented in tabular form (table 2) and show a similarity to those recorded in the first case.

Repeated studies of thick blood smears for trypanosomes and malarial parasites revealed no parasites. On October 23 and again on October 24, 5 cc of whole blood was inoculated into the peritoneal cavity of each

TABLE 2—Results of Hematologic Examinations (Case 2)

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Poly-morpho nuclear Leukocytes	Lymphocytes	Eosinophils	Mono nuclear Leukocytes	Blood Sedimentation Rate, Mm	Comment
October 19			4,100	66	34				
October 22			4,600	58	34	1	7		
October 24			4,150	49	51			21	
November 2	4,300,000	85	7,200	48	52				Presence of atypical lymphocytes
November 5	4,600,000	98	13,300	18	81	1			
November 7			8,300	34	66				
November 11	4,900,000	98	6,600	32	68				
November 15	4,150,000	90	6,900	47	48	5		20	
November 22								15	
December 5								10	
December 11			6,050	37	57	6			
January 4	4,050,000	90	8,100	46	52	2		14	
January 20	4,700,000	95	7,950	40	52	7	1	13	
February 5			7,000	41	53	5	1	4	
March 1	5,050,000	95	7,500	59	40	1		5	

was found in the electrocardiographic studies. These showed that the irregularities of rate and rhythm were chiefly due to ventricular extrasystoles and second degree auriculoventricular block. Occasional beats showed delayed intraventricular conduction.

Rapid changes in the degree of block were noted from day to day and on several occasions from hour to hour. No reasonable explanation for these could be determined, and they did not seem to represent or coincide with any other physical findings or to evidence any tendency toward regression or progression of the disease.

During this period, when it was apparent that progressive and severe cardiac damage was occurring, no subjective symptoms except palpitation were ever experienced by the patient. At no time were there any signs or symptoms of circulatory or cardiac failure. The blood pressure remained in the vicinity of the original determination throughout his entire stay in the hospital.

The myocardial damage, though severe, was not entirely irreversible, however, as was shown by improvement in his electrocardiographic tracings during the seventh week of his illness and by a return of the size of his heart to normal during the ninth week of his

of 2 guinea pigs. One of the animals died on November 16, and autopsy revealed groups of multiplying leishmanial forms of *T. cruzi* in the tissue and trypanosomal forms in the blood. The complement fixation reaction (Johnson and Kelser modifications of the Guerreiro-Machado test) was negative on October 23, strongly positive on November 12 and 23, positive but with falling titer on December 18 and 29 and January 9, 1944 and negative on January 19, February 4 and February 29. (These tests were performed for us at the Gorgas Memorial Laboratory by Dr. Johnson.)

The Kahn reaction of the blood serum was negative on two occasions.

The total serum protein was 6.9 and 7.5 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 1:3.

Repeated cultures of the blood showed no growth.

The heterophile antibody reaction occurred in a titer of 1:896 on November 25 and in a titer of 1:448 on December 1. It was negative on December 14.

Repeated examinations showed the urine to be normal.

Repeated roentgenographic examination of the chest revealed no consolidation, infiltration or pleural effusion. The cardiac measurements are shown in table 3.

Serial electrocardiograms were taken during the course of the patient's illness. Some of these were selected for mention in order to demonstrate the more important changes.

<sup>25</sup> Lundberg, K. R. A Fatal Case of Chagas Disease Occurring in a Man 77 Years of Age, *Am. J. Trop. Med.* 18:185, 1938.

The first tracing, taken on October 24, revealed a sinus mechanism, a rate of 89 per minute and an auriculo-ventricular conduction time of 0.16 second. The T waves were upright in leads I and II and diphasic in lead III. The precordial lead was normal. The next electrocardiogram, taken on November 4, revealed a rate of 80 per minute, flattened P and T waves and a significant decrease in the amplitude of the QRS complexes in all leads. Thereafter, serial electrocardiograms, taken on November 7, 9, 10 and 19, revealed progressive inversion of the T waves in the standard and precordial leads without any deviation of the ST segments. On November

TABLE 3—*Cardiac Measurements (Case 2)*

Date	Transverse Cardiac Diameter, Cm	Transverse Thoracic Diameter, Cm
October 19	12.3	31.2
November 12	14.5	31.1
November 19	14.2	30.6
December 18	12.7	31.2
December 30	12.9	31.2

19, the rate was 83 per minute and the auriculoventricular conduction time 0.17 second, and the T waves were more deeply inverted and coronary in appearance. The second beat in lead I of this record revealed a transient intraventricular block of the peculiar form in which the prolongation of the QRS complex is associated with a reduction of the PR interval. In this beat, the PR interval was reduced from 0.17 to 0.10 second and the QRS complex prolonged from 0.06 to 0.12 second. In the electrocardiogram taken November 22, the PR interval was recorded as being prolonged to 0.20 second, in contrast to the previous 0.17 second. This record also revealed frequent ventricular premature systoles. The tracing on November 26 revealed a normal auriculoventricular conduction time of 0.17 second, upward bowing of the ST segments and further inversion of the T waves. On December 4, the rate was 93 per minute, the PR interval 0.18 second and the T waves less deeply inverted. On December 7, the tracing revealed a prolonged auriculoventricular conduction time of 0.22 second. This had receded to 0.18 second on December 10. On December 14, the rate was 107 per minute and the PR interval 0.28 second. From December 4 to January 1, the T waves became less deeply inverted in spite of the evidence of persistent auriculoventricular heart block. The tracing on Jan. 1, 1944 revealed a first degree auriculoventricular block, with a PR interval of 0.28 second and upright T waves in leads I, II and IV. On January 23, second degree auriculoventricular block with Wenckebach's period was present. From then to the end of our period of observation, the rhythm varied between first and second degree auriculoventricular block, with transient intraventricular conduction defect.

## COMMENT

Certain features of the disease in these 2 cases should be emphasized, since they differ in some ways from those of previously reported cases.

In spite of the repeated previous observations in this area by Clark, Johnson and De Rivas on the benign character of the disease, particularly among adults, South American trypanosomiasis in Panama can constitute a serious illness for adults. To our knowledge, these are the first and only 2 instances in which this dis-

ease has been contracted by other than native-born persons in this area. Perhaps this fact explains why the disease took a more severe form in these 2 men than had been previously observed in adults.

The degree of symptomatic illness apparently has little prognostic value. The first patient appeared as severely ill as the second but completely recovered, while in the second severe cardiac damage developed. There was nothing in the past histories, the physical fitness of the 2 soldiers or in the degree of parasitemia exhibited which can explain this difference in the clinical courses observed. As in other disease agents, pathogenicity undoubtedly varies with different strains.

Articular symptoms and signs have not to our knowledge been previously described as a part of the clinical picture of Chagas' disease, but, as observed in case 1, these can be prominent manifestations of the illness.

Mazza previously emphasized<sup>9</sup> that the finding of a sustained increase in the lymphocyte count during the latter part of the acute stage of Chagas' disease appears to be of some diagnostic value. In both of our patients lymphocytosis occurred during the fourth and fifth week of the illness and continued during the next two months. In the second patient this response was more pronounced than in the first, and examination of his blood film revealed many young and abnormal lymphocytes. These, combined with the finding of a strongly positive heterophile antibody reaction of the serum, raised the question as to whether the second patient might not have also had infectious mononucleosis. There were, however, no other symptoms of this disease present.

Only repeated observations on other patients with Chagas' disease can provide an acceptable answer to the question.

It is interesting to note also that it was during the time that the complement fixation reaction began to fall in titer that the heterophile antibody reaction became negative.

An unusual degree of eosinophilia was not observed in either patient.

Although most of the published clinical reports of the cardiac damage observed in Chagas' disease in adults deal with the so-called chronic cases, it is evident from the observations made in case 2 that such damage may also occur during the acute stage of the disease in adults. Severe myocarditis during the acute stage is not necessarily limited to children, as some investigators have thought. Cardiac damage, though it may be severe, does not necessarily always produce a sudden or immediate death. Some degree of healing can occur. After five months of obser-

vation, we are led to believe that the cardiac lesions of the patient in case 2 have healed considerably and to deduce further from all clinical signs and symptoms and from the results of our laboratory studies that further progress of the disease seems unlikely. The damage incurred by the conducting pathways is apparently permanent, however, and that some degree of permanent cardiac incapacity will result is the most probable prognosis at this time.

In many respects the disease resembles acute rheumatic fever, from which it must be differentiated. Recent reports and our own experience in the past two years indicate that acute rheumatic fever is not an infrequent disease among soldiers in the tropics. The high fever, articular pains, erythematous and urticarial cutaneous lesions, tachycardia, electrocardiographic evidence of disturbance in conduction between the auricles and ventricles, abnormal T waves and roentgenologic evidence of cardiac enlargement are common to both diseases.

Our experience with fuadin in the treatment of this disease has been limited to these 2 instances. At the present time, there is no specific treatment for Chagas' disease. Since the antimony compounds are of definite value in the treatment of leishmanial forms of similar parasites and since this is the form of the trypanosome which actually causes the cellular and tissue damage, we felt justified in using this form of antimony in the treatment of our 2 patients. From the available reports, Bayer 7602 (Ac)<sup>26</sup> does not appear to offer much more in the way of therapeutic success and is apparently more toxic than fuadin.

We do not claim any remarkable therapeutic results in our 2 cases, and investigators with more experience do not think antimony preparations of much value. Clinically, its administration appeared to coincide with or cause the temperature to subside, to alleviate the articular symptoms in our first case and to bring about subjective improvement in both. Another obser-

vation suggesting antimony to have some merit is that the complement fixation reaction became negative in the second patient after its administration. If this test is at all analogous to other complement fixation tests as an indication of the progress and prognosis of a disease, this change is indicative that the infection has been eradicated although its scars are still present. Johnson's experience with this complement fixation test in Panama has been that the reaction remains positive in untreated patients for several years after the initial discovery of the parasites in the blood stream though no clinical evidence of the disease exists, thus suggesting that the infection remains present though in a latent stage.<sup>1a</sup>

#### SUMMARY AND CONCLUSIONS

The diagnosis of acute South American trypanosomiasis has been made in 2 additional cases in Panama, thus making a total of 21 cases of this disease which have been clinically studied in this area since 1931 and a grand total of 58 cases in which the diagnosis has been made. The disease occurred in young adult white soldiers stationed in this area. In contradistinction to the cases previously reported from this country observed in adults, the infection gave rise to a serious illness in both these soldiers and was more akin to the acute clinical picture as it has been described in other areas. These are the first 2 instances in which the infection has been diagnosed in other than native-born inhabitants in this country.

Serial electrocardiograms were made, and the cardiac manifestations of the disease were studied in 1 patient with acute Chagas' disease.

It is emphasized that articular symptoms and signs may occur as a manifestation of this disease and that these and many of the other features of acute Chagas' disease may closely simulate the disease pattern of rheumatic fever.

Lymphocytosis, as Mazza has previously pointed out, appears to be a laboratory finding of clinical significance in Chagas' disease.

In treatment of these 2 patients, antimony appears to have been of therapeutic value.

<sup>26</sup> Bayer 7602 (Ac) is a substance which consists of two 2-methyl-4-aminoquinoline groups joined by a diallyl malonyl group in position 6.

# SICKLE CELL ANEMIA IN WHITE PATIENTS WITH ULCERS OF THE ANKLES

## REPORT OF TWO CASES

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Sickle cell anemia, since it was described by Herrick in 1910,<sup>1</sup> has been known almost exclusively as a disease of the Negro race. However, after the report of Cooley and Lee in 1929, numerous instances of the disease have been reported in patients mostly of Greek, Sicilian and Italian extraction, thought to be without Negro ancestors.<sup>2</sup> The white patients mentioned in these reported cases have presented evidence of sickle cell anemia, including sickling, greenish yellow scleras, hepatomegaly, splenomegaly, pains in the joints arms or legs and occasionally abdominal crises. All available case histories of

the disease in the white race have failed to mention or have noted the absence of ulcerations or scars of the ankles or legs. It is our purpose to report on 2 patients from one family, 1 male and 1 female, with ulcers of the ankles and limitation of motion about the ankle joints.

The family history revealed that the grandmother on the paternal side was the first relative to have pallor and ulcers of the ankles. The parents of this ancestor were known to be of the white race, without negroid features, and died at the age of 84 and 86. The father, aged 47, and the uncle, aged 45, were pale and had had recurrent ulcerations of the ankles since childhood. The 2 patients presented evidence of sickle cell anemia, another brother had delayed sickling and a third brother was normal (fig 1).

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1 Herrick, J B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. *Arch Int Med* 6: 517-521 (Nov) 1910

2 Cooley, T B, and Lee, P. Sickle Cell Anemia in a Greek Family, *Am J Dis Child* 38: 103-106 (July) 1929. Cooke, J V, and Mack, J K. Sickle Cell Anemia in a White American Family, *J Pediat* 5: 601-605 (Nov) 1934. Clarke, F. Sickle Cell Anemia in the White Race with Report of Two Cases, *Nebraska M J* 18: 376-379 (Oct) 1933. Greenwald, L, Spielholz, J B, and Litwins, J. Sickling Trait in a White Adult Associated with Hemolytic Anemia, Endocarditis and Malignancy, *Am J M Sc* 206: 158-168 (Aug) 1943. Greenwald, L, and Burrett, J B. Sickle Cell Anemia in a White Family, *ibid* 199: 768-774 (June) 1940. Haden, R L, and Evans, F D. Sickle Cell Anemia in the White Race, *Arch Int Med* 60: 133-142 (July) 1937. Rosenfeld, S, and Pincus, J B. The Occurrence of Sicklemia in the White Race, *Am J M Sc* 184: 674-682 (Nov) 1932. Weiner, S B. Sickle Cell Anemia in an Italian Child, *J Mt Sinai Hosp* 4: 88-91 (July-Aug) 1937. Johnson, F B, and Townsend, E W. Sickle Cell Anemia, *South Med & Surg* 99: 377-381 (Aug) 1937. Sights, W P, and Simon, S D. Marked Erythrocytic Sickling in a White Adult Associated with Anemia, Syphilis and Malaria, *J Med* 12: 177-178 (June) 1931. Vance, B M, and Fisher, R C. Sickle Cell Disease, *Arch Path* 32: 378-386 (Sept) 1941. Wade, L J, and Stevenson, L D. Necrosis of the Bone Marrow with Fat Embolism in Sickle Cell Anemia, *Am J Path* 17: 47-54 (Jan) 1941. Morrison, M, Samwick, A A, and Landsberg, E. Sickle Cell Anemia in the White Race, *Am J Dis Child* 64: 881-887 (Nov) 1942. Stewart, W B. Sickle Cell Anemia. Report of a Case with Splenectomy, *ibid* 34: 72-80 (July) 1927. Ogden, M A. Sickle Cell Anemia in the White Race with Report of Cases in Two Families, *Arch Int Med* 71: 164-182 (Feb) 1943.

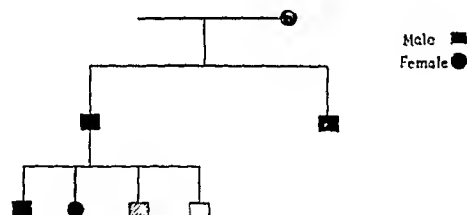


Fig 1—Family tree. Shading indicates members with ulcers of the ankles and pallor, slanting lines indicate member with sickling trait only, and white space indicates normal member.

## COMMENT

Sicklemia, a latent form of sickle cell anemia, is inherited as a mendelian dominant characteristic.<sup>3</sup> The hemoglobin content and erythrocyte counts are normal or nearly normal. Examination of a preparation of fresh blood from patients with sicklemia sealed from three to twenty-four hours reveals the presence of sickle cells. Bauer and Fisher<sup>4</sup> stated that the usual

3 Steinberg, B. Sickle Cell Anemia, *Arch Path* 9: 876-897 (April) 1930. Sydenstricker, V P. Sickle Cell Anemia, *M Clin North America* 12: 1451-1457 (March) 1929. Dreyfoos, M. Sickle Cell Anemia, *Arch Pediat* 43: 436-447 (July) 1926.

4 Bauer, J, and Fisher, L J. Sickle Cell Disease, *Arch Surg* 47: 553-563 (Dec) 1943.

hazards of sickle cell anemia may never appear in such patients during an otherwise normal lifetime

However, patients with true sickle cell anemia, children and adults, exhibit signs, symptoms and laboratory evidences of mild to profound anemia. Exacerbations and remissions occur at irregular intervals. Pallor, dyspnea, fatigue and palpitation frequently exist over a long period. A greenish yellow color of the scleras has been noted and occasionally icterus. Pains in the arms and legs may simulate those of rheumatic fever. Physical examination reveals pallor, malnutrition, evidences of hemolysis, with yellow scleras and at times enlargement of the liver and spleen, lymphadenopathy and an apical systolic murmur. Ulcers on the legs or ankles, unilateral or bilateral, have appeared in Negro patients spontaneously or after mild traumas. Healing is prolonged and followed by scarring.



Fig 2 (case 1)—Chronic ulcers of both ankles

Roentgenograms, according to Diggs, Pulliam and King<sup>5</sup> have in most cases been normal. However, they and others have described changes in the thickness of the skull, changes in the outer and inner tables and "hair on end"

<sup>5</sup> Diggs, L. W., Pulliam, H. N., and King, J. C. The Bone Changes in Sickle Cell Anemia, *South M J* 30:249-259 (March) 1937

phenomena. Osteoporosis and osteosclerosis in bones other than those of the skull are less evident.

Bauer and Fisher<sup>4</sup> and Canby, Carpenter and Ellmore<sup>6</sup> called attention to the importance to the surgeon of making a diagnosis in the absence of sickle cells in the stained blood film, since the risk to the surgical patient is increased by



Fig 3 (case 1)—Closeup of chronic ulcer of the ankle showing pigmentation and cicatrization

sickle cell anemia. Tests for delayed sickling reactions should be done in the presence of atypical medical and surgical conditions. The disease has been noted as a cause of cor pulmonale,<sup>7</sup> and occasionally in association with cholecystitis.<sup>8</sup> It has been mistaken for rheumatic fever, microcytic anemia, pernicious anemia, acute appendicitis and cholecystitis. Infectious mononucleosis has been reported in 1 patient.<sup>9</sup>

The blood picture varies from a normal or nearly normal hemoglobin content and erythrocyte count in latent sickling to a profound anemia during relapse. Sickle cells are often not found in the former stage until a wet preparation is

<sup>6</sup> Canby, C. B., Carpenter, G., and Ellmore, L. F. Drepanocytosis (Sickleemia) and an Apparently Acute Surgical Condition of the Abdomen, *Arch Surg* 48:123-125 (Feb) 1944

<sup>7</sup> Yater, W. M., and Hansmann, G. H. Sickle Cell Anemia. A New Cause of Cor Pulmonale, *Am J M Sc* 191:474-484 (April) 1936

<sup>8</sup> Schaefer, B. F. Sickle Cell Anemia and Cholelithiasis, *M Ann District of Columbia* 11:392-396 (Oct) 1942. Weens, H. S. Cholelithiasis in Sickle Cell Anemia, *Ann Int Med* 22:182-191 (Feb) 1945

<sup>9</sup> Ray, E. S., and Cecil, R. C. Infectious Mononucleosis in the Negro. Report of Three Cases with One Complicated by Sickle Cell Anemia, *South M J* 37:543-545 (Oct) 1944

sealed and left for as long as twenty-four hours, when more than 40 per cent are frequently found

Polychromatophils, erythroblasts, microcytes, macrocytes, reticulocytes and sickling of more than 4 per cent of the erythrocytes, with even more affected by a delayed sickling reaction, characterize the severe type of anemia. Target cells, erythrocytes resembling a target or bull's eye, have been described in sickle cell and other anemias<sup>10</sup>. The mean corpuscular volume may be that characteristic of either a microcytic or a macroscopic anemia. Leukocyte counts are

and palpitation on exertion, as well as pallor, fatigue and malnutrition, were known to have been present for seven years. Discoloration of the scleras had been noted, but for an unknown length of time. Moderately severe muscular pains in the arms and legs were aggravated by fatigue. There had been no abdominal crises and no known febrile attacks.

The family history revealed that the paternal grandmother, who first had ulcers of the ankles and pallor, died at 58 years of age. The father, aged 47, and the uncle, aged 45, had pallor and scarring and fixation of both ankle joints. One sister, aged 14, was extremely pale and had a small ulcer on the inner aspect of the right ankle. Two brothers had neither pallor nor ulcers (one had delayed sickling). The mother was normal. The parents of the grandmother, the first member of the

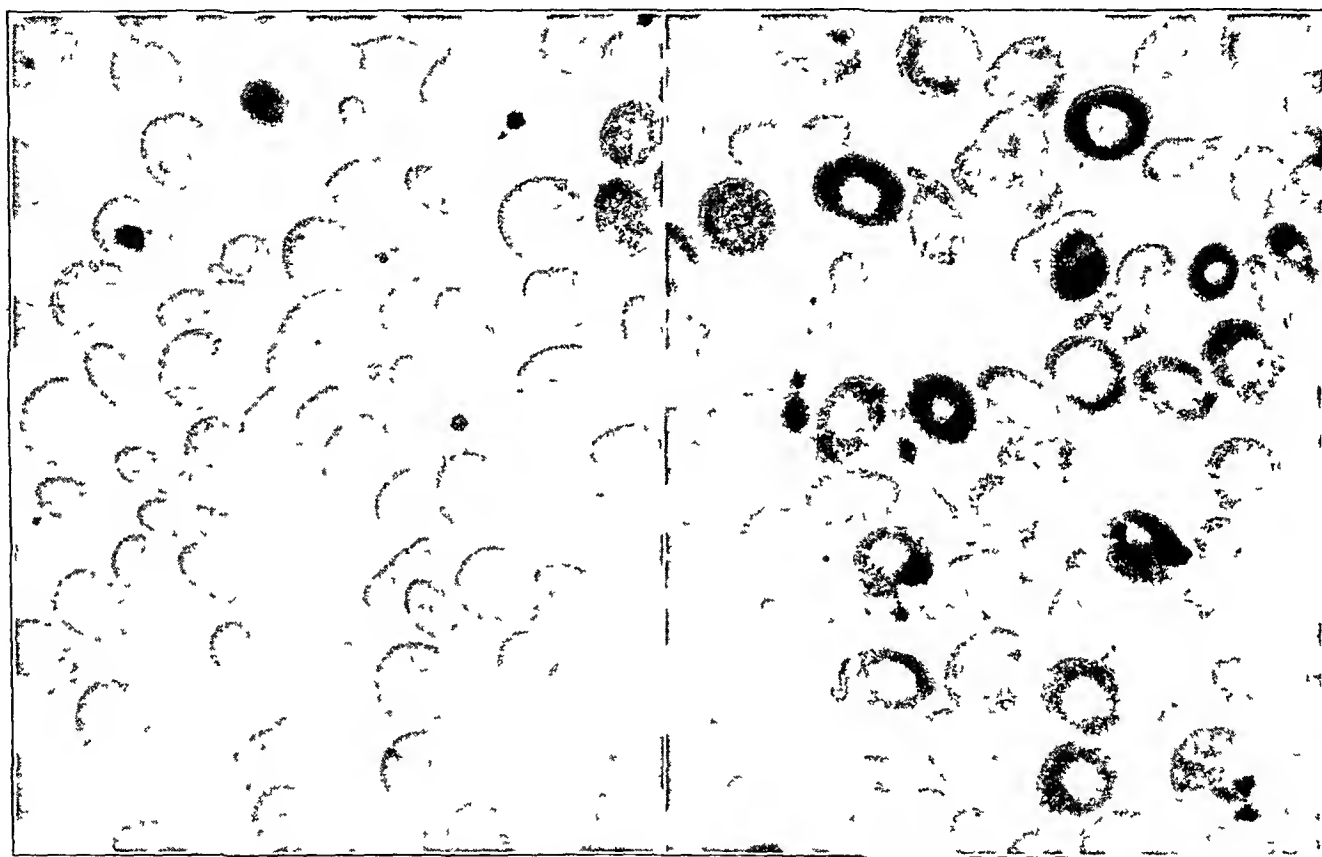


Fig 4 (case 1) —Photomicrographs of stained blood smear (not sealed)

usually elevated, with an increase in the lymphocytes and the occasional presence of 1 to 3 per cent eosinophils.

Treatment is known to have little influence on the sickling trait or the anemia. Blood transfusions may be necessary during a relapse. Rest is indicated for patients with ulcers of the ankles.

#### REPORT OF CASES

**CASE 1**—A 20 year old white youth was admitted to the hospital in August 1940, complaining of ulcers on both ankles. When he was 13, after an attack of dermatitis venenata (ivy poisoning), ulcers appeared on both ankles and have persisted until his admission. These were painful only on walking, but he had been unable to work or attend school for five years. Dyspnea

family with the disease, were known by a local historian to have been normal and of the white race.

Physical examination revealed a pallor of the lips and conjunctivas in a malnourished white youth, who seemed younger than his stated age. The skin was discolored by a pale yellow tint, and the scleras were greenish yellow. The tongue was smooth and red laterally. Both tonsils were enlarged, and there was a moderate cervical lymphadenopathy. The pulmonary fields were normal to inspection, palpation, percussion and auscultation. A systolic murmur was heard at the apex and was transmitted over the entire precordium. There was a moderate widening of the left border of cardiac dullness. The cardiohepatic angle was normal to percussion. The heart rate and rhythm were normal. A mass with a palpable notch was felt in the left upper quadrant of the abdomen 3 fingerbreadths below the costal margin. The liver was palpated 3 fingerbreadths below the right costal margin. There was no spasticity of the abdominal muscles or tenderness over any point. The knee jerks were equal on the two sides and were slightly dimin-

<sup>10</sup> Dameshek, W. Familial Mediterranean Target-Oval Cell Syndromes, *Am J M Sc* 205 643-660 (May) 1943.

ished. Sensations of heat, cold, vibration and deep tendon pain were retained. The Babinski reflex was elicited. Two large ulcers were present on the inner aspects of both ankles (figs 2 and 3).

Laboratory observations revealed hemoglobin content, 55 per cent (Sahli), red blood cells, 3,67, color index, 0.67, mean corpuscular volume, 58, platelet count, 225,040, and white blood cells, 17,850, with band forms 38 per cent, segmented forms 52 per cent and lymphocytes 10 per cent. One per cent of erythrocytes showed basophilic stippling, and 15 per cent showed sickling, increasing to 40 per cent with delayed sickling. The erythrocytes varied greatly in size and shape, including macrocytes, microcytes and many polychromatophilic cells. Most erythrocytes were pale. A few nucleated red cells were present. The corrected sedimentation rate was 9 mm in one hour, the bleeding time was three minutes. The Wassermann and Kahn reactions were negative. The urinalysis was normal, except for giving a strongly positive reaction for urobilin. Roentgenograms showed that there was no "hair on end" phenomena in the skull and that both ankle joints were normal.

CASE 2—The 14 year old sister of the first patient was seen as an outpatient with a small ulcer on the right

ankle, which had existed for approximately three weeks. Dyspnea on exertion, fatigue, pallor and malnutrition had been present since early childhood. There had been no abdominal pain or febrile attacks.

Physical examination revealed a slender, pale young white girl. Several small cervical lymph nodes were palpable. Examination showed the chest to be normal. A soft systolic murmur was heard at the apex and was transmitted over the precordium. The abdomen was normal. A small ulcer, less than 1 inch (2.5 cm) in diameter, was present on the right ankle.

Laboratory data were as follows: hemoglobin content, 60 per cent (Sahli), red blood cells, 3,77, color index, 0.75, and white blood cells, 7,4, with band forms, 16 per cent, segmented forms, 62 per cent, lymphocytes, 20 per cent and monocytes, 2 per cent. Erythrocytes varied in size and shape, including macrocytes and microcytes, and 18 per cent showed sickling. Delayed sickling increased the sickle cells to 30 per cent. The mean corpuscular volume was 75 cubic microns, the platelet count was 266,760. Hemolysis of erythrocytes began at 0.37 per cent and was complete at 0.24 per cent. The Wassermann and Kahn reactions were negative. The urine was normal. (The test for urobilin was not done.)

# CLINICAL SYNDROME IN PATIENTS WITH PULMONARY EMBOLISM

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It has been known for some time, but not generally appreciated, that pulmonary embolism may simulate many other conditions. Over thirty years ago attention was called to the fact that pulmonary embolism might be confused with pleurisy,<sup>1</sup> angina pectoris<sup>2</sup> and lobar pneumonia<sup>3</sup>. Since then the similarity between pulmonary embolism and other commonly accepted syndromes has been casually referred to in statistical studies or in individual case reports.<sup>4</sup> White<sup>5</sup> has pointed out that unexplained fainting, prostration, dyspnea, tachycardia, fever or jaundice should suggest the diagnosis of pulmonary embolism.

Failure to recognize the many clinical manifestations of pulmonary embolism may lead to erroneous diagnosis and prevent application of proper therapeutic and prophylactic procedures. In order to gain a more comprehensive view of the total clinical picture of pulmonary embolism than is now available, all cases at the Beth Israel Hospital, Boston, from 1929 to 1942, inclusive, with the diagnosis of pulmonary embolism were reviewed. Only those cases were selected in which the diagnosis was reasonably certain, the demonstration of a source of embolism was considered desirable but not essential. Of 500 cases reviewed, 108, including 32 cases studied at autopsy, were selected for study. There were 76 cases in which recovery occurred or postmortem examination was not performed. In 61 of these cases roentgenologic evidence of pulmonary infarction and/or electrocardiographic changes consistent with acute cor pulmonale<sup>6</sup> were present, and in 50 of these there was a definite source of embolism. In 9 cases, the clinical picture was consistent with pulmonary embolism and the source of embolism was demonstrable. Thus of the total of 108 cases, 102, besides showing a consistent clinical picture, satisfied any one or a combination of the following criteria: evidence at autopsy of pulmonary embolism, electrocardiographic pattern of acute cor pulmonale, roentgenographic evidence of pulmonary infarction or demonstration of the probable source of embolism. Of the remaining 6 cases, there were 4 cases of sudden postoperative death in patients under the age of 40 without any antecedent history of hypertension or cardiovascular disease, and in only 2 cases diagnosis was made entirely on the basis of the clinical picture. Cases of mitral stenosis and congestive failure, subacute bacterial endocarditis with embolic phenomena and sudden postoperative death in elderly patients without any other evi-

1 Miller, G B. The Significance of Postoperative Pleurisy. Its Relation to Pulmonary Embolism, *Am Med* **4**:173, 1902.

2 Von Neusser, E. Angina Pectoris, New York, E B Treat & Company, 1909.

3 Conner, L A. A Pulmonary Attack Simulating Primary Lobar Pneumonia, Caused by Pulmonary Embolism and Infarction from a Latent Venous Thrombosis, *Arch Int Med* **13** 349 (March) 1914.

4 (a) Hamburger, W W, and Saphir, O. Pulmonary Embolism Complicating and Simulating Coronary Thrombosis, *M Clin North America* **16** 383, 1932. Averbuck, S E. The Differentiation of Acute Coronary Thrombosis from Pulmonary Embolization, *Am J M Sc* **187** 391, 1934. Scherf, D, and Schonbrunner, E. Ueber Herzebefunde bei Lungenembolien, *Ztschr f klin Med* **128** 455, 1935. Gorham, L W. The Differential Diagnosis of Acute Occlusion of the Coronary and Pulmonary Arteries, *Albany M Ann* **55** 91, 1936. Haggard, J B, and Palmer, R S. A Case of Pulmonary Embolism Simulating Coronary Thrombosis in a Young Man Aged Thirty-Three Years, *Am Heart J* **12** 748, 1936. Pilcher, R. Slowly Fatal Pulmonary Embolism, *Lancet* **2** 942, 1938. Johnson, A S. The Antemortem Recognition of Pulmonary Embolism, *New England J Med* **222** 793, 1940. Freston, J M. Pulmonary Embolism-Diagnosis, *New York State J Med* **41** 1843, 1941. Currens, J, and Barnes, A R. The Heart in Pulmonary Embolism, *Arch Int Med* **71** 325 (March) 1943. Murnaghan, D, McGinn, S, and White, P D. Pulmonary Embolism With and Without Acute Cor Pulmonale, with Especial Reference to the Electrocardiogram, *Am Heart J* **25** 573, 1943. (b) Homans, J. Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease, *New England J Med* **229** 309, 1943.

5 White, P D. Pulmonary Embolism and Heart Disease. A Review of Twenty Years of Personal Experience, *Am J M Sc* **200** 577, 1940.

6 McGinn, S, and White, P D. Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition, *J A M A* **104** 1473 (April 27) 1935. Barnes, A R. Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, *Proc Staff Meet, Mayo Clin* **11** 11, 1936.

dence pointing to pulmonary embolism were not included. Thus, the selection of cases was rigid, and, while some cases of pulmonary embolism were undoubtedly excluded, the diagnosis in all probability was correct in the 108 cases chosen for study.

#### ANALYSIS OF DATA

The individual symptoms and signs and laboratory data observed in the 108 cases were tabulated (tables 1 and 2). Since the clinical manifestations of pulmonary embolism tend to appear

TABLE 1—*Signs and Symptoms Found in Association with Pulmonary Embolism*

Signs and Symptoms	Number of Cases (Total 108)	Number of Clinical Episodes (Total 162)
Pain		
Pleuritic	54	66
Anginal	26	37
Inadequately described	2	2
Respiratory manifestations		
Pulmonary signs	59	67
Cyanosis	36	54
Dyspnea	43	50
Cough	38	45
Tachypnea	38	43
Hemoptysis	29	34
Pleural friction rub	12	12
Signs of infection		
Fever	69	84
Chills	4	5
Cardiovascular manifestations		
Tachycardia	53	62
Fall in blood pressure	27	35
Cold clammy skin	22	30
Apprehension	14	14
Arrhythmia	7	7
Distended veins in the neck	5	5
Rise in blood pressure	2	2
Palpitation	1	1
Systolic pulmonic murmur	1	1
Pulmonary gallop rhythm	1	1
Pericardial friction rub over pulmonic area	1	1
Cerebral manifestations		
Coma	10	11
Sudden weakness	10	11
Syncope	6	6
Incontinence	3	3
Dizziness	3	3
Convulsions	2	2
Miscellaneous signs and symptoms		
Jaundice	5	5
Nausea	2	2
Vomiting	2	2
Epigastric distress	1	1
Hiccup	1	1
Muscular aches and pains	1	1

in recurring attacks or episodes, many of the symptoms and signs were present more than once in some of the patients. Each appearance of a symptom or sign or of a combination of them is referred to as a clinical episode. Certain individual symptoms and signs or combinations of them in a given patient simulated diseases or syndromes other than pulmonary embolism (table 3).

1 *Pleurisy*—Pleuritic pain occurred sixty-six times in 54 patients. There were no other symptoms or signs, with the exception of fever, in fourteen episodes, so that a diagnosis of simple

pleurisy might have been made. Hemoptysis without additional evidence except pain was present in 9 other patients. Signs of pulmonary consolidation were found in the remaining patients with pleuritic pain, the clinical picture being that of pneumonia. The development of pleural effusion was noted in 1 case. One patient had both pleuritic and anginal pain in the same episode.

TABLE 2—*Laboratory Observations*

Laboratory Test	Number of Times Test Performed	Number with Abnormal Results	Number with Normal Results
White blood cell count	92	65	27
Icterus index	24	11	13
Electrocardiogram	33	26*	7

\* In 16 cases there was the classic pattern of acute cor pulmonale,<sup>8</sup> and in 10, minor changes consistent with an incomplete pattern of acute cor pulmonale.

2 *Pneumonia*—Signs consistent with pulmonary consolidation were found sixty-seven times in 59 patients. Although in some of these the signs were equally consistent with a diagnosis of atelectasis, the high incidence of pleuritic pain (forty-three episodes) and hemoptysis (sixteen episodes) would more logically suggest a diagnosis of pneumonia. In this group vascular collapse was noted five times, clinical jaundice once and syncope once.

TABLE 3—*Syndromes Simulated by Pulmonary Embolism*

Syndrome	Number of Episodes (Total 162)
1 Pleurisy	24
Simple pleurisy	14
Pleurisy with hemoptysis	9
Pleurisy with effusion	1
2 Pneumonia	59
3 Acute heart failure	12
Dyspnea	4
Pulmonary edema	8
4 Disease of the coronary arteries	39
Angina pectoris	14
Acute myocardial infarction	25
5 Acute vascular collapse	15
6 Disease of the central nervous system	3
7 Paroxysmal rapid cardiac action	1
8 Fever of unknown origin	3
9 Sudden death	3
10 Incidental observation at autopsy	3

3 *Acute Heart Failure*—Forty-three patients had fifty episodes of dyspnea, this was the most prominent feature in twelve episodes, in four being identical with the paroxysmal dyspnea as seen in patients with heart disease and in eight being associated with pulmonary edema.

4 *Coronary Heart Disease*—Anginal pain occurred thirty-seven times in 26 patients. The character of the pain and the absence of other symptoms suggested the diagnosis of angina

pectoris in fourteen episodes, whereas the character of the pain and the associated fever, shock, dyspnea or cyanosis suggested the presence of acute myocardial infarction in twenty-three episodes. Two additional cases in which adequate description of the pain in the chest was not available presented other features which suggested the diagnosis of acute myocardial infarction.

5 *Vascular Collapse*—Vascular collapse (shock) was present in forty-two clinical episodes, in fifteen being the only clinical manifestation. Associated phenomena in the other 27 cases were pulmonary edema in 3, the clinical picture of acute myocardial infarction in 18, of pneumonia in 5 and manifestations referable to the central nervous system in 1.

6 *Manifestations Referable to the Central Nervous System*—Eleven clinical episodes were characterized by sudden loss of consciousness. In six episodes the picture was that of syncope, but in five of these subsequent evidence suggested the diagnosis of angina pectoris, pneumonia or acute vascular collapse. Of the 5 remaining cases 2 showed additional signs (such as convulsions) leading to the clinical impression of a cerebral vascular accident.

7 *Paroxysmal Rapid Cardiac Action*—Tachycardia occurred sixty-two times in 53 patients. In 7 of these the rhythm was irregular. This phenomenon was present either as the sole clinical feature of an episode (1 case) or in conjunction with one or more of the other manifestations already described.

8 *Fever of Unknown Origin*—Fever of variable duration was the sole clinical manifestation of pulmonary embolism in 3 patients and for 1 of these the diagnosis of pulmonary embolism was first made at autopsy.

9 *Sudden Death*—Sudden death, without the prior recognition of any symptoms or signs, occurred in only 3 patients.

10 *Incidental Observations at Autopsy*—Unsuspected pulmonary embolism was found at autopsy in 3 patients who died of other causes.

#### COMMENT

The clinical course of pulmonary embolism is punctuated by a series of events, and in the intervals between these there may be a complete absence of abnormal signs. These events may be thought of as attacks or clinical episodes consisting of the sudden appearance of one or more symptoms (tables 1 and 3) with or without abnormal physical or laboratory signs. The peculiar combination of these symptoms or signs or the

sudden appearance of a single one may result in the diagnosis of angina pectoris, syncope, paroxysmal rapid cardiac action and so forth. Clinicopathologic correlation has shown, contrary to our expectation, that each episode does not necessarily represent a separate pulmonary embolism. One embolus may be associated with repeated clinical episodes, or there may be fewer clinical episodes than the number of emboli which can be recognized at autopsy. The explanation for this discrepancy is not available, but possibly it may be found in reflexes arising from inflamed veins or in arteries lodging emboli.

Fatal pulmonary embolism uncommonly occurs without previous signs or symptoms, and the data clearly show that the source of emboli in the great majority of cases is the peripheral venous system (table 4). In order to prevent fatal embolism by the application of therapeutic

TABLE 4—*The Source of Embolism*

Source	Number of Cases	Evidence
Veins of the leg	60	Definite evidence of thrombophlebitis
	20	Presumptive (no clinical mention of thrombophlebitis and no heart disease)
Veins of the arm	2	Definite evidence of thrombophlebitis
Pelvic veins	5	Postmortem evidence
Mural cardiac thrombus	2	Suggestive clinical evidence
	3	Postmortem evidence
	6	Suggestive clinical evidence of heart disease and no evidence of peripheral thrombophlebitis

measures that are or may become available, it is necessary to recognize the significance of the numerous warning symptoms or signs. The diagnosis should be made, or at least suspected, even though the only manifestations of pulmonary embolism are such common events as paroxysmal rapid cardiac action or what appears to be syncope. Pleuritic pain, especially in association with other manifestations, may indicate the correct diagnosis, but anginal pain, so common in pulmonary embolism, may be misleading and obscure the diagnosis. The data indicate that anginal pain occurs more commonly in association with pulmonary embolism than has been recognized. It is a good rule to consider seriously pulmonary embolism, in addition to other conditions, whenever a diagnosis of myocardial infarction is made but not firmly established. Early in the course of myocardial infarction the temperature is normal, whereas in pulmonary embolism it is elevated, as a rule, with the onset of pain. Brief episodes of syncope or vascular collapse are much more common before the onset of pain in pulmonary embolism than in myocardial infarction. Intensification of pain by in-

spiration, with or without objective evidence of pleurisy, may occur with the outset of pain in pulmonary embolism but rarely occurs at a comparable stage in myocardial infarction. Anginal pain is apparently equally common in men and women with pulmonary embolism, in contrast to the sexual disparity in coronary heart disease. Anginal pain in pulmonary embolism may occur in patients without coronary heart disease or be absent in those with coronary heart disease, but almost one half of the patients in our series with anginal pain during pulmonary embolism had a past history of angina pectoris or acute myocardial infarction, and this fact may obscure the differential diagnosis. The incidence of anginal pain in pulmonary embolism is not influenced by the age of the patient.

Pulmonary embolism should also be considered in cases of pulmonary edema, sudden vascular collapse, cerebrovascular accidents and acute heart failure and as a possible diagnosis in cases of fever of unknown origin. Not infrequently a diagnosis of acute heart failure is made and pulmonary embolism is overlooked. The absence or paucity of signs in the heart and lungs in such cases should encourage one to elicit other signs and symptoms.

It is not necessary to consider the diagnosis of pulmonary embolism every time a patient faints or has a paroxysm of auricular fibrillation. Much depends on the background. Suspicion should be aroused, however, by these events in patients who have been immobilized by illness or operations and in those with histories of vascular disease or of trauma or infection, no matter how trivial in a leg (table 5). Homans<sup>4b</sup> has recently presented a series of cases of pulmonary embolism occurring in ambulatory patients from "silent" thrombosis of the veins of the leg. Unexplained vascular collapse, even if of short duration, should strengthen the suspicion of pulmonary embolism, particularly as more and more of the symptoms and signs listed in table 1 can be elicited. It is obvious that pain, dyspnea, tachycardia, fever, pulmonary signs and vascular collapse are common in pulmonary embolism, and hemoptysis is absent in many cases. Some of the manifestations of pulmonary embolism, such as pericardial friction rub or gallop rhythm over the pulmonic area, although uncommon, are of great importance in diagnosis and should be looked for carefully. Demonstration of a dilated pulmonary artery by physical examination or by roentgen examination may also aid in the diagnosis. When a diagnosis of pulmonary embolism is being considered on the basis of such simple events as paroxysmal auricular fibrillation

or syncope, the definite presence of phlebitis greatly increases the probability that pulmonary embolism has occurred. But it is probably of greater importance that the diagnosis of pulmonary embolism should not be discarded merely because the presence of phlebitis cannot be established. Of the 108 cases studied here the source of embolism in 90 was presumably from thrombophlebitis of the deep veins of the leg. In only two thirds of these was there definite clinical evidence of an active phlebotic process. In a number of cases conclusive signs in the legs became apparent several days after the initial episode of pulmonary embolism, even though they were diligently searched for previously. In a number of cases peripheral thrombophlebitis was probably overlooked, because the legs of the patients were not examined daily. The possibility of phlebothrombosis occurring in the absence of thrombophlebitis<sup>7</sup> must also be considered and may explain the paucity of abnormal physical signs in

TABLE 5—*Factors Predisposing to Embolism*

Predisposing Factor	Number of Cases
Operation	64
Nonsurgical diseases	14
Trauma to an extremity	6
Thrombophlebitis in patients with peripheral vascular disease	24

the legs of patients who presumably have been having repeated pulmonary emboli from veins of the leg. In patients with heart disease or with changing rhythms the heart must be considered as a possible source of the embolism, and in patients who have had pelvic operations thromboses may develop in the pelvic veins from which clots may break off. Demonstration, therefore, of a possible source of embolism is strong evidence for pulmonary embolism, but the absence of any demonstrable source, especially of peripheral thrombophlebitis, does not necessarily rule it out. From a statistical point of view it is probably correct to say that a diagnosis of peripheral phlebitis should be made when pulmonary embolism has been diagnosed, irrespective of signs in the legs, and from a therapeutic point of view it is important to realize that the phlebitis is often bilateral.

Laboratory studies may be of considerable help in diagnosis when considered in conjunction with the clinical picture. Abnormal roentgenograms are commonly found but require expert knowledge for proper interpretation. The absence of

<sup>7</sup> Ochsner, A., and DeBaakey, M. Thrombophlebitis and Phlebothrombosis, *South Surgeon* 8:269, 1939.

confirmatory roentgenographic evidence does not rule out pulmonary embolism, because infarction may not have occurred or, if present, may be located in an area of the lung not accessible to adequate examination. The electrocardiographic pattern of acute cor pulmonale is distinctive, and if electrocardiograms are taken early and repeated at frequent intervals the number of cases in which definite help in diagnosis will thus be obtained will be considerably higher than one would anticipate on the basis of reports in the current literature. In this series the pattern of acute cor pulmonale was found in approximately 50 per cent of the cases in which electrocardiograms were taken. The white blood cell count is usually elevated after pulmonary embolism but not necessarily so, for in 30 per cent of the episodes in which this determination was made there was no leukocytosis. Slight elevation of the icterus index may be a clue lead-

ing to the diagnosis of pulmonary embolism. The laboratory thus aids greatly in making the diagnosis of pulmonary embolism, but embolism can occur in the absence of abnormal roentgenographic or electrocardiographic changes and without icterus or leukocytosis.

#### SUMMARY

One hundred and sixty-two episodes associated with pulmonary embolism in 108 cases were analyzed, and it was found that the total clinical picture simulated pneumonia, angina pectoris, acute myocardial infarction, pleurisy, vascular collapse or acute heart failure in a large percentage of the cases. In a much smaller group the clinical picture was that of fever of unknown origin, paroxysmal cardiac arrhythmia, cerebral vascular accident or syncope. The problem of differential diagnosis was studied.

# Progress in Internal Medicine

## BLOOD

### A REVIEW OF THE RECENT LITERATURE

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In this review of the current literature on hematology up to 1945, an effort has been made to include foreign articles published during the past several years which have not heretofore been available in this country. Review of articles in more readily available publications is limited to those appearing during 1944, unless it has appeared that through oversight an important article has failed to receive attention in previous reviews. Although as comprehensive a coverage of the literature as possible has been attempted, limitations of personnel and facilities have made certain omissions inevitable. These, it is hoped, may be corrected in future reviews. It has been a source of surprise and gratification that in spite of the obvious obstacles to research so many significant investigative projects were successfully carried out both in this country and abroad.

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#### PERNICIOUS ANEMIA

*Etiology*—It is stated by Castle<sup>1</sup> that beef muscle, milk, eggs, liver, yeast, rice polishings and wheat germ are known to contain the so-called extrinsic factor for the hemopoietic reaction with normal human gastric juice (the intrinsic factor). Using the technic which he has previously employed of testing material by incubating it with normal human gastric juice and administering the product to patients with pernicious anemia, he found that the careful purification required to render crude casein vitamin-free is also essential for the elimination of the extrinsic factor. Furthermore, it was observed that the addition of thiamine, riboflavin, nicotin

<sup>1</sup> Castle, W. B., Ross, J. B., Davidson, C. S., Burchenal, J. H., Fox, H. J., and Ham, T. H. Extrinsic Factor in Pernicious Anemia. Ineffectiveness of Purified Casein and of Identified Components of the Vitamin B Complex, *Science* **100**: 81, 1944.

amide, pyridoxine hydrochloride, dicalcium pantothenate, paraaminobenzoic acid, choline hydrochloride, *L*-inositol, biotin, xanthopterin and folic acid to casein so extracted gave no evidence of the reconstitution of the extrinsic factor activity of the crude casein. He concluded, however, that it is nevertheless reasonable to continue to regard the extrinsic factor as the thermal stable component of the vitamin B complex, as yet unidentified.

The theory has previously been advanced by Agren<sup>2</sup> that the intrinsic factor of Castle might be identical with the enzyme aminopolypeptidase. This is based on the observation that the injection of crystalline secretin intravenously into cats provoked a secretion from the distal part of the pyloric region and the proximal part of the duodenal region which contained a high concentration of aminopolypeptidase. It was demonstrated further that an enzymic action (proteolysis) took place after this secretion was incubated with muscle extract. Furthermore, while preparing the enzyme from the pyloric mucosa of hogs it was found that purified enzyme solutions apparently contain most of the intrinsic factor activity present in the mucous membrane. The author states he has now purified the enzyme to about a hundred times. Evidence that the aminopolypeptidase is the intrinsic factor is based on the assumption that if the intrinsic factor activity can be shown to parallel that of aminopolypeptidase the conclusion that the latter may be identical with the intrinsic factor would be favored. While this may be suggestive evidence, it certainly would not be entirely convincing. Clinical results which the investigator obtained on 4 patients suggested this relation. He states that a detailed report will appear in the *Acta Medica Scandinavica*.

Careful consideration is given by Askey<sup>3</sup> to the hypothesis that pernicious anemia may be of dietary origin. The rather startling statement is made that if dietary deficiencies cause Addisonian pernicious anemia then they must also explain the natural distribution and natural history of the typical form of the disease. This is a conclusion which in our minds does not seem to be entirely permissible. In evaluating the relation of the dietary factors in patients with pernicious anemia, Askey sets up rather high standards as diagnostic criteria. For example, the diagnosis of pernicious anemia is not abso-

lutely acceptable to him unless there is a primary composite triad of essential criteria consisting of (1) a permanent histamine-refractory anacidity, (2) a permanent reduction of Castle's intrinsic factor and (3) a reduction of the stored anti-pernicious-anemia principle. While his arguments favoring the rigidity of the criteria in evaluating patients with macrocytic anemia are, undoubtedly sound, nevertheless, they are not practical. Askey considers that the natural history of pernicious anemia is indicated by an orderly development of anacidity, loss of intrinsic factor and loss of anti-pernicious-anemia liver principle. While this theory may be correct, it certainly is an assumption. He cites convincing evidence to indicate that there is no relation between the natural distribution of the disease and poor nutrition. For example, in China and Java, where malnutrition is common, pernicious anemia is almost unknown. He also states that, although no precise data regarding the diets of patients with pernicious anemia over long periods are available, there is no evidence to indicate that there is an inadequate intake of food except in the periods just before the manifestations of the disease appear. We have been interested in this problem since 1927 and made an extensive analysis, which was not published, of the dietary habits of a fairly large group of patients with pernicious anemia and compared this with a similar analysis of a control group with various other diseases. There was no difference between the two groups. In discussing the question "can dietary deficiencies produce Addisonian pernicious anemia?" Askey<sup>4</sup> cites the prevalence of macrocytic anemia in many Mohammedan women of India, who live on diets largely vegetarian, high in carbohydrate and low in protein and in natural vitamins of the B complex. As this type of anemia does not respond to purified Dakin-West anti-pernicious-anemia fraction (Anahaemin), he concludes that it apparently is not due to a deficiency of specific anti-pernicious-anemia principle. Likewise, concerning sprue, he states that hydrochloric acid is often found in the gastric juice and that the intrinsic factor may also be present. It apparently is his opinion that dietary deficiencies cannot produce characteristic Addisonian pernicious anemia. Although he agrees that tropical macrocytic anemia, pellagra and sprue respond to the injection of liver extract, he objects to the acceptance of this information as proof that these diseases are identical with Addisonian pernicious

<sup>2</sup> Agren, G. Nature of the Anti-Anaemic Factor (Castle), *Nature*, London **154** 430, 1944.

<sup>3</sup> Askey, J. M. Dietary Factor in Etiology of Pernicious Anemia, *Ann Int Med* **21** 402, 1944.

<sup>4</sup> Askey, J. M. Addisonian Pernicious Anemia Without Achlorhydria. Does It Exist? *Gastroenterology* **2** 1, 1944.

anemia. He rejects it because, he claims, the Cohn fraction G liver extract is usually employed in the treatment of such patients and this contains two distinct anti-macrocytic-anemia principles, namely (1) the specific pernicious anemia principle and (2) the anti-macrocytic-anemia principle effective against tropical macrocytic anemia. In brief, Askey concludes that deficient diets in human beings over a period of years may produce macrocytic anemias but not commonly the mechanism operative in Addisonian pernicious anemia. In a survey of the literature relating to the production of the essential features of pernicious anemia in experimental animals by dietary deficiency, Askey concludes that only in hogs has the essential triad of objective signs been produced by a defective diet. He concludes that such a condition has been produced by Miller and Rhoads.<sup>5</sup> It is his opinion, however, that dietary deficiencies which produce the essential objective triad of pernicious anemia in members of a remote species, hogs, fail to produce pernicious anemia either in members of the nearest related species to human beings, monkeys, or in human beings themselves. He does not regard these experiments, therefore, as being of crucial significance.

In a discussion of the racial distribution of pernicious anemia, Askey concludes that when the racial factor is constant in any particular area of the world and the climatic factor is variable varying results occur. It is his opinion, therefore, that climate is of secondary importance to race in producing the incidence of pernicious anemia. He believes that racial factors best explain the natural geographic distribution of the disease. It is his final opinion that the natural distribution, which is racial, geographic and climatic, can be adequately explained by hereditary factors.

A résumé of the literature dealing with the late effects of total and subtotal gastrectomy has been given by Ingelfinger.<sup>6</sup> Various aspects of disturbed physiologic function following removal of the stomach are considered by Ingelfinger, but only those relating to the development of anemia will be discussed here.

He asks "Why do not patients with gastrectomies, particularly those with total gastrectomies, have pernicious anemia?" He goes on to

say, however, that as a matter of fact a small number of patients do, but in his opinion the development of true pernicious anemia is an extremely rare sequela. He points out, however, that in 1941 Meyer, Schwartz and Weissman<sup>7</sup> collected 54 cases of what they considered to be authentic pernicious anemia following total gastrectomy. Since that time another case has been reported by Rhodes and Grunberg.<sup>8</sup> It is pointed out by Ingelfinger that before one can assert that true pernicious anemia occurs as a sequel to gastrectomy control periods during which the patient receives extrinsic factor and is observed by means of reticulocyte counts before and during liver therapy, adequate follow-up periods and possibly even studies of the bone marrow are necessary. In his opinion, even if the evidence for pernicious anemia is unequivocal, the possibility still exists that in some cases pernicious anemia following gastrectomy is merely the results of coincidence. The relation of total gastrectomy to the development of the blood picture of pernicious anemia has been of interest to us over a considerable period of years. Certainly, if the hypothesis of Castle is true, then the removal of the entire stomach should be followed by the development of a blood picture of pernicious anemia. This undoubtedly occurs in some cases, but it sometimes does not appear until after a period of two to four years has elapsed. When one considers that the operation for total gastrectomy is even now not a common one, but is becoming more so, and that in the past many of the patients did not survive the operation over a few days and some not over a few months, it is not surprising that only a relatively small number of cases can be recorded. It is our tentative belief, which may be revised depending on the subsequent observations, that the complete removal of the stomach of any human being will ultimately be followed by the development of the blood picture of pernicious anemia if the patient is followed over a period of years and does not receive anti-pernicious-anemia therapy. With the increasing frequency of this operation, the answer to this important question should be learned within the next few years.

A report on total gastrectomy of 73 patients, of whom 24 failed to survive, giving an operative mortality of 33 per cent, is published by Lahey

<sup>5</sup> Miller, D. K., and Rhoads, C. P. The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, *J. Clin. Investigation* **14**: 153, 1935.

<sup>6</sup> Ingelfinger, F. J. Late Effects of Total and Subtotal Gastrectomy, *New England J. Med.* **231**: 321, 1944.

<sup>7</sup> Meyer, K., Schwartz, S. O., and Weissman, L. H. Pernicious Anemia Following Total Gastrectomy, *Arch. Surg.* **42**: 18 (Jan) 1941.

<sup>8</sup> Rhodes, A. J., and Grunberg, A. Macrocytic Anemia Following Partial Gastrectomy, *Brit. M. J.* **1**: 726, 1943.

and Marshall<sup>9</sup> Of the last 28 patients on whom gastrectomy was done, however, only 5 died, which figure represents a mortality rate for that group of 18 per cent It is undoubtedly true that total gastrectomy for gastric carcinoma will become a more common operation in the future as an increasingly large number of patients are being reported on on whom this operation has been performed This is of special interest to the hematologist, as it creates an experimental condition which should throw considerable light on Castle's hypothesis in relation to the etiologic importance of the intrinsic factor of the stomach to the development of pernicious anemia A brief reference is made in this paper to the appearance of anemia following the operation, the sole statement being "In spite of the loss of all the gastric tissue, the primary type of anemia has not been encountered after total gastrectomy Postoperative secondary anemia is a frequent complication to be watched for, and, when it does occur, the patient should be put on a regular maintenance dose of liver extract parenterally" The increasing frequency of gastrectomy, therefore, raises an interesting question which will undoubtedly be decided by further observations Why does not complete anatomic extirpation of the stomach, which is responsible for the formation of the intrinsic factor, always produce pernicious anemia? This question is asked by Askey<sup>4</sup> It is known that patients may survive for years following total gastrectomy without the development of pernicious anemia Allen<sup>10</sup> reported on 1 patient alive and well with a normal blood picture four and one-half years after total gastrectomy It would seem that if the stomach is the site of the manufacture of the intrinsic factor after its removal there must be either a large store of this material or of the erythrocyte-maturing factor somewhere in the body Another possibility is that the intrinsic factor may be manufactured elsewhere, although with the present state of knowledge there is no information which has a bearing on this particular point It has been shown by Geiger, Goodman and Claiborn<sup>11</sup> that total gastrectomy in swine pro-

duces exhaustion of the supply of anti-pernicious-anemia principle in the liver Now information bearing on this point is available in human beings who had a total gastrectomy some years ago Certainly, if the opportunity offers, this observation should be obtained

A comprehensive review of the literature relating to the stomach and erythropoiesis and also to the etiologic role played by the stomach in producing both hypochromic and hyperchromic anemias is given by Wollheim<sup>12</sup> In addition, he presents some of his own experimental observations on rabbits and dogs and discusses his conclusions relating to the etiology of pernicious anemia and to the normal control of erythropoiesis

*Achlorhydria in Pernicious Anemia*—When one reports a case of pernicious anemia in which it is claimed that hydrochloric acid is present in the gastric juice, it becomes necessary, in the opinion of Askey,<sup>1</sup> first, to exclude all the possible causes of macrocytic anemia, second, to demonstrate the absence of the intrinsic factor, and, finally, to prove that the anemia is due to a deficiency of the specific anti-pernicious-anemia liver factor Cirrhosis of the liver, extreme hypothyroidism, pregnancy, sprue, pellagra, gastric neoplasm, intestinal strictures and anastomoses and gross nutritional deficiencies are all adequate causes for macrocytic anemia These must be excluded before the diagnosis of true pernicious anemia is acceptable According to Askey, a reduction in the gastric intrinsic factor may be associated with pregnancy, gastric neoplasm, sprue, intestinal strictures, ulcers and avitaminosis, and the mechanism of the loss of the intrinsic factor in these conditions is not the same as in Addisonian pernicious anemia To be significant, therefore, the loss of the intrinsic factor must be shown to be idiopathic by the exclusion of the other conditions which may induce it It is recognized by Askey that it is impracticable to demonstrate reduction in the specific liver principle Direct studies by biologic assay of the liver can be made only in the fatal cases Indirect data obtained by the response of the patient to the administration of liver extract are not entirely acceptable, according to this investigator In his opinion, the liver extract usually used is Cohn's fraction G, which contains not only the specific anti-pernicious-anemia principle but also different fractions which have been shown to be effective in nutritional macro-

<sup>9</sup> Lahey, F H, and Marshall, S F Indications for and Experience with Total Gastrectomy, Based on Seventy-Three Cases of Total Gastrectomy, *Ann Surg* **119** 300, 1944

<sup>10</sup> Allen, A W Total Gastrectomy for Carcinoma of Stomach, *Am J Surg* **40** 35, 1938

<sup>11</sup> Geiger, A J Goodman, L S, and Claiborn, L N Effects of Gastro-Intestinal Resections in Swine on Anti-Anemia Potency of Liver, with Observations on Nature and Sources of Materials Effective in Pernicious Anemia, *Yale J Biol & Med* **13** 259, 1940

<sup>12</sup> Wollheim, E Magen und Erythropoese, *Schweiz med Wchnschr* **73** 233, 1943

cytic anemia of the tropics. According to him, it is impossible to know, therefore, whether improvement of a macrocytic anemia following the administration of Cohn's fraction G is due to the specific anti-pernicious-anemia fraction or the fraction effective against nutritional macrocytic anemia. He suggests that if the response to liver is used as a therapeutic test a favorable effect is of little significance unless the Dakin-West product or one of the other highly purified fractions obtained from the original Cohn's fraction G is used. He assumes that a determination of the response to desiccated hog stomach (Ventriculin) would be a more precise and accurate therapeutic test.

In a consideration of 47 reports in the literature of cases of pernicious anemia without achlorhydria, he has concluded that 32 of these cases are unacceptable because other causes for the anemia were present or because the data were unconvincing. It is his final opinion that it has never been established beyond doubt that Addisonian pernicious anemia can exist with persistence of secretion of hydrochloric acid. The diagnosis of Addisonian pernicious anemia, therefore, without achlorhydria has been a presumption, not an established fact. It is his opinion that the existence of true pernicious anemia without anacidity as yet cannot be accepted. In this belief we are in complete accord. Certainly, the presence of hydrochloric acid in the gastric secretions of patients suspected of having pernicious anemia casts serious doubt on the diagnosis, and some other explanation of the associated macrocytic anemia should be sought.

A gastric analysis was done on 418 general medical patients in Bombay, India, by Bhende,<sup>13</sup> and it was found that 84 of them had achlorhydria. Seventy-nine of these patients had anemia, and hence it was apparent that the anemia contributes most frequently in this particular area to achlorhydria. These patients, in fact, were admitted to the hospital primarily for treatment of the anemia state. Analysis of the types of anemia are as follows: true achlorhydria, as indicated by the absence of free hydrochloric acid following the injection of histamine, 44; pernicious anemia, 19; tropical macrocytic anemia, 13; idiopathic hypochromic anemia, 5; normocytic anemia of varied origin, 4; hook worm infection, 1; pellagra, 1, and carcinoma of the stomach, 1. There were 35 patients classified as having false achlorhydria, that is, patients who had no free hydrochloric acid after a test meal. Of these patients,

7 secreted acid after the administration of dilute alcohol and the remainder required the maximum stimulus of histamine for the demonstration of hydrochloric acid. Thus, in 28 of 72 patients with anemia, or 38.8 per cent, acid was found in the gastric contents only after the injection of histamine. There were 31 patients with false achlorhydria, classified as tropical macrocytic anemia, 1 with idiopathic hypochromic anemia, 2 with normocytic anemia of varied origin, and 1 with normocytic anemia with cirrhosis of the liver. The author emphasizes that histamine stimulus must always be employed to distinguish true from false achlorhydria. He also points out that some patients with tropical macrocytic anemia do not exhibit true achlorhydria.

A comprehensive consideration of achlorhydria in patients with anemia is given by Moschcowitz.<sup>14</sup> He discusses the incidence of achlorhydria in apparently normal persons, and the relation of achlorhydria to idiopathic hypochromic anemia, to pernicious anemia, to the anemia of pregnancy, to the anemia of myxedema, to the anemia of sprue and to the anemia of gastric carcinoma. A statement is made which we challenge, namely, that pernicious anemia may develop in persons with hydrochloric acid in the stomach. The reference to the work of Askey abstracted in this review is of interest in this connection. The discussion by Moschcowitz, however, is exceedingly thorough, and a bibliography of fifty-eight articles is appended.

It has been reported by Davis<sup>15</sup> that the daily oral administration of 5 Gm of soybean lecithin to dogs resulted in a reduction in the red blood cell count which persisted for at least ten days after cessation of the lecithin feeding. He also observed that choline hydrochloride in daily oral doses of 8 mg per kilogram of body weight caused a significant depression in the number of erythrocytes in dogs. The action of choline in this case was explained by its assumed depressing effect on erythropoiesis caused by the increased blood flow and oxygen supply to the bone marrow through its vasodilator action.

Studies have also been made by Davis<sup>16</sup> which, if verified, would provide a mechanism for the

14 Moschcowitz, E. Essays on the Biology of Disease. The Biology of Achlorhydria in Relation to Anemia, *J Mt Sinai Hosp* 10:796, 1944.

15 Davis, J. E. Depression of Normal Erythrocyte Number by Soybean Lecithin or Choline, *Am J Physiol* 142:65, 1944.

16 Davis, J. E. Experimental Production of Hyperchromic Anemia in Dogs Which Is Responsive to Anti-Pernicious Anemia Treatment, *Am J Physiol* 142:402, 1944.

13 Bhende, Y. M. Achlorhydria and Anaemia. An Analysis of Seventy-Nine Cases, *Indian M Gaz* 77:13, 1942.

evaluation of anti-pernicious-anemia medication. He produced a hyperchromic anemia in dogs by the oral administration of three doses daily of choline chloride, 10 mg each per kilogram of body weight. This resulted in moderate to mild anemia in the animals. He believed that the anemia was the result of a depression of erythropoiesis. It is of great interest to note that the intramuscular injection of adequate doses of purified solution of liver extract in 3 of the dogs caused an increase in the number of red blood cells, with a return to normal in approximately four weeks. These responses continued in spite of administration of choline. Powdered stomach U S P, fed in daily doses of 20 Gm to 1 mildly anemic dog, caused a return of the red blood cells and hemoglobin percentage to normal within twelve days in spite of continued choline feedings. These experiments, if confirmed, are of the greatest importance and deserve careful consideration by all hematologists.

Davis<sup>16</sup> gave 60 Gm of lard and 10 mg of choline hydrochloride per kilogram of body weight daily to 4 normal dogs and observed the effect on the circulating blood. He found that there was a rapid significant reduction in the erythrocyte count, associated with an elevation of the icterus index. It was his opinion that the fat caused anemia by increasing hemolysis and that the choline feeding alone would not produce a significant fall in the erythrocytes until it had been administered for eight or more days. It was his belief that the choline acted by causing vasodilatation and improved blood and oxygen supply to the bone marrow, thus depressing erythropoiesis. As he expressed it "Choline acted as a weak brake to inhibit any acceleration of erythropoiesis which may normally follow the hemolytic destruction of red blood cells."

It has been noted by Johnson, Freeman and Longini<sup>17</sup> that the lacteal lymph collected close to the small intestines of dogs after a fatty meal is strongly hemolytic. They assumed that the hemolytic action was due to the action of free fatty acids which had failed to be resynthesized. This observation led to a series of experiments in which they demonstrated that exposure of normal human red blood cells to lipemic serum renders those cells more susceptible to hemolysis by distilled water or by soap solutions. They concluded, therefore, that these experiments suggest that the destruction of an appreciable part

of red blood cells in normal human beings might be accounted for by the injurious effects of ingestion of fat, although bone marrow seems fully able to compensate for these losses of red blood cells. It occurred to them, however, that an increase in this destructive effect of ingested fat might be responsible for certain human anemias. After making a number of observations on patients with pernicious anemia, they concluded that in patients with untreated pernicious anemia the ingestion of fat is more injurious to red blood cells than it is in treated patients with pernicious anemia or in normal persons. Their experiments also led them to conclude that the fragility of the erythrocytes is increased by exposure to normal lipemic serum. These observations strongly suggested to the observers that the ingestion of fat may injure the red blood cells sufficiently to contribute significantly to the anemia of pernicious anemia and that an abnormal sensitivity of the red blood cells to the products of fat absorption may be an etiologic factor in this type of blood disorder. The authors review the evidence supporting the concept that hemolysis is at least a factor in causing the anemia of pernicious anemia and state that evidence is accumulating to the effect that liver extract acts in anemia generally by protecting the erythrocytes from excessive hemolysis. They also note that liver therapy has been demonstrated to protect red blood cells against hemolysis and also to be curative in the anemia produced in animals by indole plus a deficient diet. This fact is supported by their experimental evidence that ingestion of fat injured the red blood cells in patients with untreated pernicious anemia more than in normal persons or in patients with treated pernicious anemia. It is their opinion that the evidence presented in this paper would seem to provide a basis for attempts to control or improve the condition of patients with pernicious anemia by a diet that is as nearly fat-free as possible.

These observations are of interest and open up a new field which may be of great importance and have a significant bearing on the cause of pernicious anemia as well as the cause of other types of hemolytic anemia.

Previous literature dealing with the possible association between the relative lack of solar radiation and the mortality rate from pernicious anemia is reviewed by Thiersch<sup>18</sup>. It has been stated that there is a significant relation between the relative lack of solar radiation and the mor-

17 Johnson, V, Freeman, L, and Longini, J. Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, *J A M A* 124 1251 (April 29) 1944

18 Thiersch, J B. Solar Radiation and Pernicious Anemia in South Australia, *M J Australia* 1 583, 1944

tality rate from pernicious anemia in the United States and that this is also true concerning the disease in Europe. Furthermore, in 1942 Apperly<sup>19</sup> came to the conclusion that the mortality rate of pernicious anemia and the amount of solar radiation were inversely related. The studies by Thiersch, however, do not confirm this view. He concludes that there was no evidence found in South Australia to confirm the hypothesis that an inverse relation existed between the incidence of pernicious anemia and the degree of solar radiation. While the number of cases of pernicious anemia in South Australia corresponds closely to that in England, in relation to the population, the occurrence of cutaneous cancer in South Australia is far greater than that in the British Isles. The increase is due mainly to the greater solar radiation, as the localization of the cutaneous cancers on the face and hands indicates.

It is emphasized by Jasinski<sup>20</sup> that the condition of the bone marrow in both patients with sprue and patients with pernicious anemia is identical. Furthermore, this investigator states that in the presence of an iron deficiency anemia the fully developed picture of pernicious anemia may be inhibited.

*The Diagnosis of Pernicious Anemia*—It is stated by Rossi<sup>21</sup> that many cases of pernicious anemia do not present the classic clinical picture but often have a vague symptomatology. He presents as an example the following clinical forms, all of them atypical: (1) febrile, (2) septicemic, (3) intestinal, (4) gastric, (5) jaundiced, (6) nervous. In each one of these forms, he states, the diagnosis of pernicious anemia was made after a study of the blood and the bone marrow.

A case of a 20 year old youth who was said to have had pernicious anemia is discussed by Carrera Dominguez<sup>22</sup>. In this case the most outstanding features of the clinical history were those referred to the gastrointestinal tract, namely, vomiting, great loss of weight, sore tongue and a tendency to diarrhea. Physical examination showed pallor, mitral stenosis and slight splenomegaly. The red blood cell count was 1,380,000

per cubic millimeter and the color index 1.63. The white blood cell count was 3,200 per cubic millimeter. The serum bilirubin level was 1.6 mg per hundred cubic centimeters of serum. There was achlorhydria present. The patient made a good recovery with liver therapy. The author describes this case because of the outstanding complaints referable to the gastrointestinal systems. He gives a brief discussion of the presence of such symptoms in patients with pernicious anemia.

A general article dealing with the clinical picture and the diagnostic points of pernicious anemia is presented by McNamara<sup>23</sup>.

*The Nervous System in Cases of Pernicious Anemia*—The clinical and pathologic observations in 2 cases of pernicious anemia with subacute degeneration of the brain and spinal cord are described by Adams and Kubik<sup>24</sup>. They emphasize that the cause of the degeneration of the nerve fiber in such cases is obscure but suggest that a deficiency of some substance other than the intrinsic factor may account for it. It is also pointed out that lesions involving the cerebrum are less well known than are the changes in the spinal cord and that they are not even mentioned in many textbooks on neurology. In each of their 2 cases there were well defined neurologic and psychiatric symptoms, which serve as a basis for their discussion. In their opinion the lesions of the cerebrum and of the spinal cord are almost exactly alike and consist of diffuse, although uneven, degeneration of the white matter with little or no proliferation of the fibrous glia. This similarity suggests that the degeneration of the cerebral white matter is specifically related to pernicious anemia as is subacute combined degeneration of the spinal cord. The neurologic changes which occur in patients with pernicious anemia are unique and quite unlike those that are present in patients with cerebral vascular disorders, multiple sclerosis, encephalitis and other more chronic degenerative diseases. They differ from those observed in pellagra, because in the latter condition, although there is degeneration in the columns of Goll throughout their course, this process is not uneven as in pernicious anemia and because in pellagra there is a pronounced gliosis. The authors point out an interesting sequence of events which has been observed by us on more than one occasion. In their opinion the changes

19 Apperly, F. L. Relation of Pernicious Anemia to Solar Radiation in Skin Cancer, *Am J M Sc* **203** 854, 1942.

20 Jasinski, B. Das Verhalten des retikuloendothelialen System des Knochenmarkes bei der Perniziosa- und Sprue-Erythropoese, *Schweiz med Wchnschr* **74** 188, 1944.

21 Rossi, R. Formas disimuladas de anemia perniciosa, *Rev argent-norteam cien med* **1** 343, 1943.

22 Carrera Dominguez, P. Notas hematologicas con motivo de un caso de anemia de Biermer, *Medicina, Madrid* (pt 2) **11** 77, 1943.

23 McNamara, F. P. The Clinical Diagnosis of Pernicious Anemia, *J Iowa M Soc* **34** 242, 1944.

24 Adams, R. D., and Kubik, C. S. Subacute Degeneration of Brain in Pernicious Anemia, *New England J Med* **231**.1, 1944.

in the spinal cord usually, if not invariably, precede the changes in the brain, in fact the order of development of involvement of the central nervous system is as follows: first the posterior columns, then the lateral and anterior columns and finally the cerebral white matter. They refer to an interesting article by Bertrand and Ferraro<sup>25</sup> in which it is reported that in a patient with gastric carcinoma and macrocytic anemia there were lesions of the brain and spinal cord exactly similar to those observed in patients with pernicious anemia. They cite such a case as an example of the fact that subacute degeneration may be associated with conditions other than pernicious anemia. Although there is a difference of opinion about this matter as expressed in various articles in the literature, they believe that patients with lesions of the brain have mental symptoms, whereas the converse is not necessarily true, as cerebral lesions have not always been found in patients with mental symptoms. They conclude by stating that they favor the supposition that both subacute combined degeneration of the spinal cord and subacute degenerative lesions of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary to the metabolism of myelinated nerve fibers. They do not think that every patient with pernicious anemia will have demonstrable lesions of the brain, but it is their belief that all those in whom there are definite and widely disseminated lesions of the brain will probably have mental disorders.

*Other Diseases Associated with Pernicious Anemia*—Two cases of thyroid dysfunction associated with pernicious anemia are reported by Charaton<sup>26</sup>. One patient was a woman of 62 years who had a nodular goiter with severe anemia which had all the characteristics of pernicious anemia. This responded to treatment with crude liver extract and later with desiccated hog stomach. The thyroid condition was treated with strong solution of iodine U.S.P. (Lugol's solution). The patient improved strikingly, and the red blood cell count came to normal. Thyroidectomy was refused. The second patient was a woman of 68 years who, he says, had the classic features of myxedema, although no basal metabolic rate or cholesterol estimation was re-

ported. There was no question that she had a severe anemia with a red blood cell count of approximately 1,400,000 and a hemoglobin content of 44 per cent. There was achlorhydria following the injection of histamine. With administration of desiccated thyroid, 1 gram (0.06 Gm) twice daily, and crude liver extract, 2 cc intramuscularly, striking improvement resulted. The question arises here as to whether she might not have had a severe macrocytic anemia of myxedema rather than pernicious anemia, although the two diseases have been reported previously as coexisting in the same patient. In such patients the elevation of the blood cholesterol may have been of importance, as it is always elevated in patients with myxedema in our experience.

According to Woolley<sup>27</sup> the term "leukanemia" was first introduced by Leube in 1900. It was considered to be a condition characterized by a leukemoid blood picture accompanied with a macrocytic hyperchromic anemia. It is likely, however, that leukanemia in the earlier literature indicated a condition which was usually an aleukemic leukemia or pernicious anemia with a leukemoid blood reaction. Woolley considers that the term does not designate a separate disease entity but is used for purely descriptive purposes and thus may be likely to give rise to confusion. The case of a patient who had pernicious anemia and in whom outspoken myelogenous leukemia later developed is reported by Woolley. This patient was first seen in 1932, at which time she was 48 years of age, and she then had the characteristic clinical picture of pernicious anemia. There was achlorhydria and a characteristic reticulocyte response to anti-pernicious-anemia medication. Ten years later the typical picture of chronic myelogenous leukemia developed, with a white blood cell count of 85,600 per cubic millimeter and characteristic immature white blood cells. In addition to the great increase in the white blood cell count and the presence of a high percentage of primitive leukocytes, there was enlargement of the spleen to about 6 inches (15 cm) below the left costal margin. Roentgen ray therapy caused a reduction in the leukocytes and in the size of the spleen. It is possible that the two diseases may occur in the same patient as a result of a constitutional predisposition of the hemopoietic system. The author concludes, however, that the cause of the association of the two diseases in the same person is unknown but that the association probably is coincidental.

25 Bertrand I, and Ferraro, A. Contributo alla conoscenza dell'anatomia patologica della degenerazione sub-acute combinata del midollo spinale, *Cerebello* 4, 1, 1924.

26 Charaton, F. B. Pernicious Anemia Associated with Thyroid Dysfunction. Two Cases, *St Thomas Hosp Gaz* 42, 94, 1944.

27 Woolley, P. B. Myelogenous Leukemia Complicating Pernicious Anemia, *Lancet* 1, 85, 1944.

MACROCYTIC ANEMIA RELATED TO  
PERNICIOUS ANEMIA

Two cases of deficiency anemia in infants are reported by Bass,<sup>28</sup> 1 of which was corrected by the use of liver extract and the other by hydrolyzed casein. It is emphasized by Bass that in the majority of instances severe anemia in early infancy is due to a deficiency of iron but that an anemia may be due also to an inadequate supply of other substances concerned with the production of hemoglobin. Bass states that the anemia has been described in some of the reports in the literature as macrocytic, resembling pernicious anemia in adults, and that in others the condition is described as being similar to a hypochromic anemia due to iron deficiency. He reports 1 case of its occurrence in a 6 month old infant with a red blood cell count of 920,000 per cubic millimeter and a hemoglobin content of 17 per cent. This anemia was refractory to iron but responded to injections of liver extract with an increase in the reticulocytes to 16 per cent and a rapid return of the hemoglobin content and red blood cell count to normal. The second case was that of a 5 month old infant who had a severe anemia which did not improve after long-continued treatment with iron and frequent blood transfusions. In this case, however, cure was obtained by the administration of hydrolyzed casein known to contain the essential amino acids. It is of interest to note that anemia developed in this infant at a time when goat's milk had been substituted for cow's milk on account of an allergy to the latter. A full discussion of the anemia associated with the diet of goat's milk is given.

It is pointed out by Davis<sup>29</sup> that pernicious anemia in the first two decades of life is an extremely rare condition. He cites reviews of the literature which include a survey of 1,532 cases of pernicious anemia, with only 4 of the patients being under 20 years of age. He doubts if any of the published cases of pernicious anemia in children have met the rigid diagnostic criteria of that condition. Nevertheless, he states that in a number of the cases the anemia was hyperchromic and macrocytic and responded to liver therapy. He considers this evidence that the anemias were megaloblastic in nature. Three cases of severe megaloblastic anemia in children 12, 13 and 14 years old were reported. The

evidence in all 3 cases against a diagnosis of true Addisonian pernicious anemia is the failure to respond typically to liver extract therapy, the presence of free hydrochloric acid in the gastric contents and the temporary nature of the blood condition. In conclusion Davis states that, although the blood and sternal marrow pictures were typical of pernicious anemia, there was convincing evidence against the acceptance of this diagnosis. In his opinion, the condition may have resulted from defective assimilation from the alimentary tract. It is of interest that 2 of the 3 patients in these cases responded to proteolyzed liver administered orally after it had been demonstrated that they were refractory to parenteral injections of liver extract of known potency.

It is reported by Seelig and Hemming<sup>30</sup> that Indian soldiers on field service in whom malaria developed were commonly found to have severe macrocytic anemia. The observations in 23 cases are summarized. They stated that the patients' skins were pale, with a lemon tint, and that the tongues were smooth, atrophic and suggestive of Hunter's glossitis in pernicious anemia. Studies were not made on the hydrochloric acid content of the gastric secretions. The livers and spleens were palpable in all patients but not greatly enlarged. Lymph nodes were normal. All patients came from a malarious area, and each had had fever with rigor within two or three months of his admission to the hospital or had malarial parasites (malignant tertian or benign tertian) in the blood when admitted. Patients had had no antimalarial treatment or the treatment was inadequate or intermittent. Examination of the blood showed severe megalocytic anemia, with considerable anisocytosis and poikilocytosis, frequent punctate basophils, small and large nucleated red cells and leukopenia. All showed well defined hypochromasia. The serum bilirubin level did not exceed 1 mg per hundred cubic centimeters in any case. The number of red cells averaged between 2,000,000 and 3,000,000 although in some instances the anemia was more severe. One patient was reported as having a red blood cell count of 560,000 per cubic millimeter. The authors considered that the anemia was probably of a nutritional macrocytic type which was precipitated by the inadequately treated malaria. Treatment was carried out with iron, liver and a full diet, and the results were satisfactory.

<sup>28</sup> Bass, M. H. Deficiency Anemia in Infants. Report of Two Cases with Associated Temporary Deficiency of Antianemia Factor in One and Allergy and Abnormal Digestion of Protein in the Other, *Am J Dis Child* 67:341 (May) 1944.

<sup>29</sup> Davis, L. J. Macrocytic Anemia in Children, *Arch Dis Childhood* 19:147, 1944.

<sup>30</sup> Seelig, S. F., and Hemming, J. R. Megalocytic Anaemia as a Sequel to Malaria, *Lancet* 1:498, 1944.

Macrocytic anemia as it occurs in natives of New Guinea is reported on by Giblin<sup>31</sup>. He states that his notes, which cover the twenty years from 1921 to 1941, were written from the point of view of a casual clinical worker and from memory. The macrocytic anemia seen in natives of New Guinea is characterized by the following signs: (1) relatively acute onset with pyrexia, which may last weeks or months, (2) rapid enlargement of the spleen, which is both painful and tender but diminishes in size during spontaneous remission, (3) blood picture of macrocytic anemia, (4) rapid loss of weight, and (5) spontaneous remissions and relapses. He states that there is also a more chronic type of macrocytic anemia, in which the spleen is enlarged but not painful. The anemia is of low grade, is compatible with reasonably good health and is amenable to liver therapy. The course is nonfebrile. For some unknown reason, the anemia may at times become more active. Giblin observed about 20 cases during the twenty years from 1921 to 1941. Most of the patients were young men. In his opinion, malaria does not enter into the clinical picture as a cause, because most of the natives have acquired a full immunity to this disease.

The general subject of anemia in pregnancy is discussed by Roberts<sup>32</sup> who states that three main types are found: physiologic anemia, iron deficiency anemia and pernicious anemia of pregnancy. He reports 2 cases of the last type. He states that the macrocytic anemia induced by pregnancy is certainly not established as a separate entity. According to him, few cases have been investigated with thorough hematologic technique. He states that it is said to differ from Addisonian pernicious anemia in that achlorhydria is rare and spontaneous recovery usually occurs after parturition. Changes in the cord are not seen. True pernicious anemia complicated by pregnancy is rare, because the age incidence is such either that patients have borne their children or that their fertility is so lowered by the anemia that they are incapable of bearing more. He reports, however, the case of 1 patient who had a child when she was 22 years of age. Her symptoms of pernicious anemia began when she was 33 years of age, and she conceived again some four years after her blood count had returned to normal. He states that judging by the dose of liver extract required to keep

her in good health pregnancy did not seem to have affected her condition adversely. A second patient with pernicious anemia had also some evidence of iron deficiency. This patient had not conceived during the first eight years of her married life and did not do so until three years after her blood picture was first restored to normal. Her labor was complicated also by mitral stenosis, but there was no evidence of cardiac failure. As with the previous patient, the dose of liver extract required to keep her in good health remained the same after pregnancy.

The occurrence of severe megalocytic anemia in a 20 year old male vegetarian is reported by Cook<sup>32a</sup>. The patient's diet was adequate in calories, as indicated by his state of general good nutrition, but was obviously deficient in animal protein. The hemoglobin content was 35 per cent, the red blood cell count 1,400,000 per cubic millimeter and the white blood cell count 10,600 per cubic millimeter. The mean diameter of the erythrocytes was 8.2 microns. Hydrochloric acid was absent in the gastric secretions after injection of histamine during the stage of severe anemia but later appeared. There was a striking response to the injection of liver extract.

A fatal case of achrestic anemia in a 56 year old woman studied at necropsy is reported by Huse<sup>32b</sup>. The diagnosis was based on the finding of a macrocytic anemia which failed to respond to efficient anti-pernicious-anemia medication and a megaloblastic hyperplasia of the bone marrow. Achlorhydria was present, which was attributed to an associated chronic gastritis. No attempt was made to test for the presence or absence of the antianemic principle in the liver, but the author considered that sufficient evidence was present without this information to substantiate the diagnosis of achrestic anemia.

*Treatment, Including Pernicious Anemia*—A comprehensive article on the treatment of the chronic anemias by Reznikoff<sup>33</sup> may be read with profit by any one coming in contact with patients who have anemia. Reference will be made to the treatment of the macrocytic anemias only. He warns that to treat anemia with "shot gun" therapy is usually uneconomical and often results in failure. Iron should be given only for iron deficiency states, liver therapy for macrocytic

31 Giblin, W. E. Some Clinical Notes on Macrocytic Anemia in New Guinea Natives, *M. J. Australia* 1 89, 1944.

32 Roberts, G. F. Pregnancy in Pernicious Anemia, *St. Barth. Hosp. J.* 48 53, 1944.

32a Cooke, R. T. Megalocytic Anaemia in a Young Vegetarian, *Brit. M. J.* 1 558, 1944.

32b Huse, A. A. Achrestic Anaemia with Achlorhydria, *Brit. M. J.* 1 184, 1944.

33 Reznikoff, P. Treatment of the Chronic Anemias, *M. Clin. North America* 28 368, 1944.

anemia and transfusions to treat anoxia and as a palliative measure. According to this author, with whom we agree, unless a patient has a macrocytic anemia or one entirely or in part due to a lack of intrinsic or extrinsic factor, there is no justification for the use of liver extract. Furthermore, if there is no reticulocyte response in five to ten days or a conspicuous rise in the number of red blood cells within two or three weeks after the beginning of therapy, the continued use of liver therapy is not indicated. We are in agreement with his emphatic statement that the intramuscular injection of liver extract is the route of choice for administration and that only for a rare patient who is sensitive to parenteral treatment should oral therapy be considered. He recommends that the average patient with pernicious anemia receive 15 to 30 U S P units of an accepted liver extract intramuscularly daily until the reticulocyte peak is reached—that is, for a week to ten days. After this, the frequency of the injections may be decreased to three times a week until the red blood cell count reaches 4,000,000 per cubic millimeter. He agrees that the maintenance dose varies rather widely, some patients may need only 15 units a month and a few need as much as 15 units a week. Infections, neurologic signs and symptoms and possibly arteriosclerosis may alter the amount of the maintenance dose. He warns that a patient who has paresthesia, diminished vibratory sense and other signs of neurologic involvement should receive more therapy than a subject free from these. He also advises that such patients should take large amounts of vitamin B for their peripheral neuritis.

Sippe<sup>34</sup> treated a large number of patients with nutritional macrocytic anemia whom he encountered in Mauritius. This condition was particularly common in members of the community who did not include beef flesh in their diet for religious reasons. The anemia occurred in both sexes and was most prevalent during the second and third decades. It was especially apt to appear in the latter half of pregnancy. In patients who also had malaria and splenomegaly, the disease was probably aggravated by the excessive destruction of normal and abnormal erythrocytes by the hypertrophied reticuloendothelial system. A number of patients with nutritional macrocytic anemia were successfully treated with yeast obtained locally as a waste product in the manufacture of alcohol by the

fermentation of molasses. The potency of the material obtained from the distilling vats was due to the presence of autolyzed yeast, which contains one or more factors necessary for the normal maturation of red blood cells and in whose absence an anemia of the macrocytic type develops.

A scholarly discussion of the etiologic factors responsible for the production of pernicious anemia and of the bearing which spontaneous remissions may have on this subject is given by Bloomfield<sup>35</sup>. He contends that a study of the spontaneous remissions and other data which he presents supports the toxic hemolysis theory of pernicious anemia rather than the concept of deficiency of material necessary for the maturation of red blood cells. Evidence is cited to indicate that true spontaneous remissions actually occur and that they are not the result of inadvertent ingestion of antianemia materials. Furthermore, he contends that spontaneous remissions are not readily explained on the deficiency theory but are compatible with the theory of intermittent action of a toxic substance. He shows that transfused blood disappears during a relapse, whereas it is "held" during remission. Furthermore, he emphasizes that there are variations in the maintenance dose of effective antianemia material from time to time in the same patients and that they are difficult to explain on the basis of deficiency but are compatible with the toxic hemolysis theory. He also points out the interesting fact that many elderly people have a deficient gastric secretion and presumably an inadequate supply of Castle's intrinsic factor, yet they fail to acquire pernicious anemia. Furthermore, he points out that total gastrectomy is certainly not always followed by the development of pernicious anemia as one would anticipate if Castle's theory were entirely correct. Certainly his arguments are thought provoking and merit careful consideration by all persons interested in the disease.

Myers<sup>36</sup> summarizes his experience in dealing with 85 cases of pernicious anemia and discusses various diagnostic and therapeutic problems. He emphasizes that in 6 per cent of his patients with pernicious anemia carcinoma of the stomach developed and states that one might anticipate a much higher percentage since both conditions begin with gastric atrophy. He mentions, among other things, that gallbladder disease is not uncommonly associated with pernicious anemia,

35 Bloomfield, A. L. The Spontaneous Remission of Pernicious Anemia. Its Bearing on the Nature of the Disease, *Stanford M. Bull.* 2, 5, 1944.

36 Myers, F. Vagaries in Diagnosis and Treatment of Pernicious Anemia, *Ohio M. J.* 40, 635, 1944.

34 Sippe, G. R. Autolyzed Yeast in the Treatment of Nutritional Macrocytic Anemia, *Brit. M. J.* 1, 656, 1944.

but one wonders whether there is an etiologic relation. It is stated that 4 of his patients had myxedema and that a combination of desiccated thyroid and anti-pernicious-anemia medication is required to bring these patients to normal. Intrigued by the occurrence of pernicious anemia in a husband and wife, he asks the question "Is pernicious anemia a dietetic or a marital failure?" It is his opinion that oral therapy is not as effective as parenteral and should never be recommended for patients with neurologic symptoms. He concludes that 84 per cent of his patients were improved with treatment, 2 per cent were unimproved and 14 per cent died. Changes in the spinal cord still present the greatest problem in the treatment of this disease, and the response to intensive therapy is still far from satisfactory. According to him, vitamin B complex and nicotinic acid are of doubtful value.

Important studies relating to the incidence and causes of relapses in pernicious anemia have been made by Schwartz and Legere<sup>37</sup>. Their report is based on the observations on 54 patients with 88 individual self-induced relapses brought about by discontinuance of anti-pernicious-anemia therapy, either immediately after release from the hospital or months or even years after a satisfactory maintenance dose had been established. All their patients were from an economic level below average and dependent in part for subsistence on various forms of financial aid. For the most part, their diets were suboptimal in animal proteins, vitamin B factors and vitamin C. It is obvious, therefore, that these observers were dealing with a type of patient who was most likely to have a relapse when therapy was inadequate. The patients who discontinued therapy returned in a state of relapse at intervals varying from two to thirty-eight months. About one third of them had relapses during the first six months, approximately another third in the next six months, about 24 per cent in the second year, 5 per cent in the third year and 1 per cent later. They were unable to correlate such factors as sex, age, race, total amount of liver administered, duration of treatment before discontinuance and average monthly dose with the "relapse period". Patients with pernicious anemia who require relatively small amounts of liver extract to maintain a normal blood level may have relapses in as short a time as two months after the therapy is omitted. Studies dealing with the "depot method" of administration of large amounts of liver extract at one time indicate

that there is some storage of the liver principle when massive quantities are given, but this is not a quantitative storage. It is the opinion of these observers that the factor of relapse is a highly singular phenomenon which is remarkably inconstant, even in the same patient. They believe the "individual relapse period" is probably intimately linked with the quantitative secretion of the "intrinsic factor," the quantity of "extrinsic factor" and of other essential dietary factors and the storage of the "anti-pernicious-anemia principle" in the liver. This analysis probably does not tell the entire story, since there is no correlation between the "relapse time" and the average amount of liver necessary for maintenance. It is suggested that a cyclic change may take place in the glands of the stomach which secrete the intrinsic factor and that such changes may account for the variability of the relapses and of the individual liver requirements from time to time. They conclude that previous studies which have attempted to evaluate massive dose therapy and the storage of liver extract are inaccurate because sufficient cognizance is not taken of the highly individualized behavior of patients with pernicious anemia during remissions.

A summary concerning 80 living patients with pernicious anemia who have been under treatment for variable periods is presented by Hardgrove, Yunk, Zotter and Murphy<sup>38</sup>. There was a possible family history of anemia for 12.5 per cent of the patients. The majority of their patients, approximately two thirds, were derived from German, Polish and Irish stock, and 1 was a Negro woman. It is of interest to note that in 14 per cent of the patients the hair became dark after treatment. The correct diagnosis of pernicious anemia was made during the first year of illness for only 36.25 per cent. For 53.75 per cent the diagnosis was not made by the first physician consulted, and for 86 per cent it was not adequately established until hospitalization. As is true in most groups of patients with pernicious anemia, the most common initial symptoms were weakness and fatigue. Sore tongue occurred at the onset in 56 per cent, paresthesias in 71 per cent, disturbance in the gait in 41 per cent, disturbance of the bladder in 42.5 per cent and gastrointestinal complaints in 82.5 per cent. Heart disease of a degenerative type was present in 33.7 per cent. Satisfactory maintenance of the red blood cell count and body weight were obtained in 66 per cent of the patients by one in-

<sup>37</sup> Schwartz, S. O., and Legere, H. Relapses in Pernicious Anemia, *J. A. M. A.* **124**: 637 (March 4) 1944.

<sup>38</sup> Hardgrove, M., Yunk, R., Zotter, H., and Murphy, F. Summary of Eighty Living Cases of Pernicious Anemia, *Ann. Int. Med.* **20**: 806, 1944.

jection of 3 cc of crude liver extract (15 units) every four weeks and in 11.5 per cent by one every three weeks. For individual patients more frequent injections were required. Allergic reactions to liver extract were prominent in this series, as they were reported to occur in 27.5 per cent of the patients and in 5 compelled a change to oral therapy. As is usual for patients receiving treatment for pernicious anemia, some had relapses. Nineteen patients in this group discontinued treatment for periods of three months to five years, but all subsequently resumed it. The time elapsing before severe relapse occurred varied greatly for different patients.

The normal serum level of cholesterol was determined by Nayar,<sup>39</sup> as was the level of the cholesterol in anemia and also the effect of cholesterol therapy in various types of anemia. He found the blood level of cholesterol in Indians to be lower than that in Europeans, as indicated by a maximum of 152, a minimum of 100 and a mean of 126 mg per hundred cubic centimeters in nonpregnant natives of India. In pregnant women of India the maximum blood level of cholesterol is given as 247, the minimum as 112 and the mean as 179.5 mg. He observed that the blood cholesterol level is low in persons suffering from any type of anemia, irrespective of the variety. In some instances the blood cholesterol is reported to be as low as 66, 58 or 25 mg per hundred cubic centimeters. In 1 instance it was 20 mg. These observations seem to be unbelievably low. It was not thought that the blood cholesterol level runs parallel with the red blood cell count or the hemoglobin concentration of the blood. Furthermore, he concludes that infections, bacterial, protozoal and helminthic, seem to lower still further the blood cholesterol level of anemic persons. The effect of cholesterol therapy on anemia is discussed. The patients were given intramuscular injections of 5 per cent solution of cholesterol in olive oil, 2 cc daily or on alternate days. Various types of anemia were treated, but 40 patients out of the 51 studied presented a macrocytic hyperchromic blood picture, 5 were orthochromic and normocytic, and the remaining 6 were hypochromic and microcytic. Of the 45 patients with macrocytic hyperchromic and normocytic orthochromic anemia, 41 were pregnant and 4 were nonpregnant. He concluded that cholesterol did not take the place of liver in the treatment of patients with tropical macrocytic anemia but that the combination of cholesterol with liver therapy in treatment of the severely ill patients with macro-

cytic anemia of pregnancy might be better than liver alone. In treatment of tropical macrocytic anemia in nonpregnant patients, cholesterol supplements the hemopoietic action of iron to a certain extent, but even in such cases improvement is much more rapid with liver therapy. He states that the blood cholesterol level is low in all cases of severe anemia, irrespective of pregnancy.

Young and Bett<sup>40</sup> emphasize correctly the fact that a laboratory method for the determination of potency of liver extracts intended for the treatment of patients with pernicious anemia would be of great value. They review the method reported by Overbeek and his associates,<sup>41</sup> in which explants of bone marrow from normal guinea pigs are cultured in a solid medium of saline solution and heparinized plasma. In this medium, cells, which are chiefly leukocytes, migrate from the explants to form a reasonably clearcut zone of migration. According to them, the addition of an active liver extract is said to stimulate the migration. A modification of this method has been utilized by Young and Bett. They report their conclusions as follows. They are unable to confirm reports of a quantitative or qualitative relation between the occurrence of "a peak" in migration of cells from normal guinea pig bone marrow grown in the medium mentioned. According to them, peak migration does not take place consistently at any dilution from 1:100 to 1:300,000 of extracts of known anti-pernicious-anemia activity but occurs irregularly whether or not liver extract is present. Furthermore, they conclude that little if any added stimulation by purified extract occurs. There is no difference, therefore, which is sufficiently definite and which can be used as a basis of any methods of assay.

According to Davis and Allinson,<sup>42</sup> previous studies have shown that experimental polycythemia may be produced in dogs by the feeding of raw liver or by the injection of purified solution of liver and by the feeding of choline hydrochloride. The authors undertook an investiga-

40 Young, C. M., and Bett, H. D. Bone Marrow Procedure for Assay of Liver Extracts for Anti-Pernicious Anemia Activity, *J. Pharmacol. & Exper. Therap.* **81**: 248, 1944.

41 Overbeek, G. A., Gaillard, P. J., and de Jongh, S. E. Ein qualitatives und quantitatives Testverfahren für die Wirkung antianämischer Leberextrakte in vitro, *Schweiz. med. Wchnschr.* **68**: 711, 1938. Gaillard, P. J., Overbeek, G. A., and Yam, T. H. Action of Anti-anemic Preparations on Bone Marrow in Vitro, *Arch. internat. de pharmacodyn. et de thérap.* **64**: 33, 1940.

42 Davis, J. E., and Allinson, M. J. C. The Presence of a Choline-Like Substance in Several Injectable Solutions of Liver, *Proc. Soc. Exper. Biol. & Med.* **54**: 266, 1943.

39 Nayar, S. Cholesterol and Anaemia, *Indian M. Gaz.* **77**: 459, 1942.

tion for the purpose of determining whether highly purified solutions of liver extract for parenteral use contain any choline or choline-like activity. After studying six injectable liver extracts, they concluded that each one contained choline or choline-like substances which on acetylation produced vasodepressor activity which was antagonized by atropine.

*Sensitivity to Liver Extract*—A matter of increasing importance to all physicians who administer anti-pernicious-anemia medication is the occasional occurrence of various "reactions" to this type of treatment. The most comprehensive review dealing with this subject is one written by Kaufman, Farmer and Reich<sup>43</sup>. They record that since 1931 there have been thirty-five articles dealing with this subject, in which a total of 50 patients are reported as having experienced reactions from liver extract by injection. In addition, they report on 11 patients, 4 of which were seen personally by them and 7 whose detailed histories were provided by other physicians. While reactions to various types of anti-pernicious-anemia medication are not common, nevertheless they are observed in every large hematologic clinic and are likely to occur in the experience of all physicians who give liver extract intramuscularly. There have been a few reports of allergic reactions from the oral ingestion of liver, either raw or cooked, or of liver extract, but reactions most commonly occur when the medication is given intramuscularly. It may follow the use of almost every type of liver extract, including the European preparations. It is also known that when patients experience a reaction from one brand they are likely to have the same untoward effect from other preparations. To a certain extent, the amount of extract injected is of importance, but this is not always true. It is known that a reaction may occur locally after a test dose with as minute an amount as 0.1 cc of a 1:1,000 dilution intracutaneously. On the other hand, it has been observed that a patient may have a reaction when 1 cc of Reticulogen (liver extract with added thiamine hydrochloride) is given subcutaneously, whereas this effect did not follow the injection of 0.5 cc given in the same manner. Reactions most commonly occur after the product has been well tolerated for weeks, months or even years, especially after a long interval between the injections. The authors recognize the remarkable and unexplained fact that although the patient may have

the initial reaction after numerous injections it may disappear for no apparent reason and never occur again despite a continuation of the same type of medication. The suggestion is made that these reactions may be due occasionally to inadvertent intravenous injections. Sensitivity to liver extract may persist for a long period, even up to eight years, as in 1 patient. The authors state that of the 61 patients with reactions to liver extract reported on in the literature only 6 were known to have definite evidence of allergy, 13 showed no other allergic manifestations, and concerning the remainder no statement was made. The clinical manifestations of the reactions to liver extract are exceedingly diverse. The most frequently encountered is either urticaria alone or in association with other allergic symptoms, such as pain, edema, erythema and itching. On the other hand, the reactions may be as severe as angioneurotic edema evidenced by the characteristic features of asthma. In some instances the manifestations of typical anaphylactic shock appear, such as weakness, a rapid and weak pulse, vomiting, dyspnea and a pronounced fall in blood pressure. The authors state that almost the whole gamut of allergic manifestations have been described. They report that no fatalities have occurred, although we can state that in some cases the symptoms are so severe as to suggest the possibility of an imminent fatality and 1 fatal case has been observed in England<sup>44</sup>. Of interest are the results of the intracutaneous tests performed with various brands of liver extract which are reported in the literature. The total number of patients who have had allergic reactions from liver extract who were subsequently tested intracutaneously number 26, of whom 24 showed positive results of cutaneous tests. Of 11 patients studied by Kaufman and his associates, 8 showed positive reactions. It is generally agreed that in a large majority the reactions following the oral or parenteral administration of liver extract are undoubtedly related to allergy. This opinion is supported by the clinical picture, the positive results of intradermal tests and the occasionally reported presence of reagins and precipitins. It is of interest to note that if the patients are allergic to some substance in the liver extract it is through sensitivity to the organ and not to the species of animal. For example, if a patient reacts to beef liver, it is likely that swine or sheep liver will produce the same effect. It seems reasonable to assume, therefore, that the sensitivity is to some

<sup>43</sup> Kaufman, R. E., Farmer, L., and Reich, C. Allergic Reactions to Liver Extract, *Ann Int Med* 19: 768, 1943.

<sup>44</sup> Morgans, C. C. Intolerance to Liver Extract in Pernicious Anemia, *Brit M J* 1: 613, 1943; Sensitivity to Liver, Letters and Answers, *ibid* 2: 29, 1943.

substance in liver, irrespective of its biologic source. The immediate symptomatic treatment of allergic reactions to liver extract consists of the injection of epinephrine hydrochloride (1:1,000) in a dose of 0.3 to 0.5 cc subcutaneously. If there is a local reaction, it should be treated with calamine lotion containing phenol. The simplest way to avoid reactions is to discontinue the parenteral use of liver extract and to give the patient oral anti-pernicious-anemia medication, consisting of either liver extract or powdered stomach. Although changing to oral preparations may be of value in avoiding reactions, it is generally agreed that this method of therapy is less efficacious than is the intramuscular. It has been recommended by Taylor and Higler<sup>45</sup> that histaminase may be used. They assert that results of intradermal tests with liver extract following the use of this preparation are definitely less pronounced. There is no conclusive proof, however, to indicate that the clinical reactions are reduced, and it does not seem feasible to administer histaminase constantly throughout the remainder of the period in which the patient is to take liver extracts, especially if he has pernicious anemia. It is suggested by Kaufman and his associates that a more feasible therapeutic agent for patients who react frequently might be histamine in gradually increasing doses. They also recommend that desensitization with gradually increasing doses of liver extract is an excellent method for use in treating those patients who react regularly. They suggest that the initial treatment be the subcutaneous injection of 0.1 cc of a 1:10 dilution, the dose being increased by about 0.2 cc every second or third day for about three weeks until the patient is receiving the full therapeutic dose, such as Lederle's liver extract, 3 cc, or Reticulogen, 0.5 to 1 cc. In their opinion it is important to keep this type of patient "desensitized" by administering the extract in small quantities at more frequent intervals than is customary, at least once a week. When giving liver parenterally to such patients one should have epinephrine hydrochloride and a sterile syringe and needle at hand for emergency use. They also concede that although the patients may improve, as indicated by a decreased frequency of their reactions, one must take into account the spontaneous loss of sensitivity which occasionally occurs in these patients.

<sup>45</sup> Taylor, C. B., and Higler, D. W. The Use of Histaminase by Mouth in Preventing Systemic Reactions to Parenteral Liver Extract, *J. A. M. A.* **117**: 1880 (Nov. 29) 1941.

It is stated by McSorley and Davidson<sup>46</sup> that of 16 patients with pernicious anemia admitted consecutively to their wards during the past five years, in 4, or 66 per cent, reactions subsequently developed after one to three years of maintenance by intramuscular liver extract therapy. Reactions are classified into two groups, namely, primary and secondary. The primary reactions they consider as not due to an acquired sensitivity but to an immediate response of the body to the parenteral injection of foreign material. These are more likely to occur when the preparation is given intramuscularly. Secondary reactions to oral, intravenous and intramuscular liver therapy have been described, and McSorley and Davidson believe they are undoubtedly of an allergic nature. They recognize that if a patient is sensitive to one brand of liver extract sensitivity to other products is also likely and hence the sensitivity is related to liver rather than to any species, as other investigators have thought. Although they appreciate the limitations of cutaneous reactions in relation to sensitivity to liver extract, they suggest that it is worth while to perform cutaneous tests, since it is found that in the majority of cases the degree of cutaneous reaction bears some relation to the severity of the general sensitization and of the reactions which result.

For the patients with mild reactions they believe it is permissible to attempt to control the reactions by injecting 3 minims (0.18 cc) of a 1:1,000 solution of epinephrine hydrochloride concurrently with the liver preparation. For other patients who have mild reactions they state that good results may be obtained by reducing the quantity of the injection to one half or one fourth of the dose which produced the reaction and decreasing the periods between injections by a quarter or a half. In the treatment of the patients with severe reactions, however, it is recommended that the parenteral administration of liver be replaced by oral ingestion of whole liver extract or of preparations of stomach or that desensitization be carried out. The latter procedure is recommended as cheaper and more effective than oral therapy. They warn, however, that desensitization is a potentially dangerous procedure unless carried out under strict supervision by some one familiar with the dangers of anaphylactic reactions. They refer to the 1 fatality following an allergic reaction to liver therapy, which was reported by Morgans<sup>44</sup> in the *British Medical Journal* in 1943. Using the technic which they describe in detail, they were able to

<sup>46</sup> McSorley, J. G., and Davidson, L. S. P. Sensitivity to Liver Extract, *Brit. M. J.* **1**: 714, 1944.

desensitize successfully 15 patients who had previously experienced severe reactions

It is stated by Engelhardt and Derbes<sup>47</sup> that reactions to the intramuscular injections of liver extract are not so rare as is generally thought, for they have observed several instances in a relatively short period. Various types of reactions are discussed, and the classification of Tausk<sup>48</sup> is considered. He divided the reactions into three categories: (1) erythematous reactions, (2) those associated with a fall in blood pressure or histamine-like reactions and (3) truly allergic reactions. In addition, they describe local reactions to liver extract. The authors observed a histamine-like reaction characterized by a fall in blood pressure associated with nausea which persists for half an hour or more. The patient in whom this reaction occurred had no subsequent untoward effects from liver extract by injection. They describe truly allergic reactions as being of the local type with erythema and

edema, and a severe generalized allergic reaction as being characterized by difficulty in breathing, tachycardia and loss of consciousness. They suggest that an ampule of epinephrine should be available and that the drug should be given in doses of 0.3 to 0.5 cc if necessary and that the local type of allergic reaction may be avoided by alternating the site of the injection just as one does with insulin. The statement that a substitution of one commercial product for another brand will often result in control of the untoward symptoms is not in accord with our experience or with that of other investigators who have noted reactions to liver extract. Their opinion that desensitization may be attempted but is generally unsuccessful also is not in agreement with our experience and with that of others with regard to methods of controlling reactions to liver extract. They consider that many patients may tolerate oral liver extract therapy well whereas they are sensitive to the preparations for intramuscular injection, and such is the experience of most observers. They also recognize that a change in the animal source of the liver is not apt to solve the problem, since the allergic reaction is to the liver and not to the animal.

47 Engelhardt, H. T., and Derbes, V. J. Allergy to Liver Extract, *South M. J.* **37** 31, 1944

48 Tausk, N. Bireacties na insuiting van Lever-extracten, *Nederl. tijdschr. v. geneesk.* **80** 749, 1936

*(To be Continued)*

## Book Reviews

**Arterial Hypertension Its Diagnosis and Treatment** By Irvine H. Page, M.D., and Arthur Curtis Corcoran, M.D. Price, \$3.75 Pp 352, with 14 figures Chicago The Year Book Publishers, Inc., 1945

Of the several books recently published on arterial hypertension, this one best fulfils the requirements of a general practitioner. A comprehensive study of arterial hypertension is presented with a minimum of theoretic detail. In their approach to the problem, the authors aim to study the patient as a whole, rather than to concentrate on hypertension by itself. They develop this idea in a manner which shows that they understand hypertension, the natural history of the disease, the intricate mechanisms involved and the psychic as well as the somatic reactions of the patient.

The book is divided into five sections. Sections I and II take up the definition and classification of hypertension and some phases of the examination of the patient. Sections III and IV include studies of the circulation, particularly the renal and the coronary circulation, and a clinical study of the heart and the kidneys in essential hypertension. Treatment, including therapy with drugs, treatment with endocrine substances and surgical intervention, are considered in section V. The appendix consists of a classification and a study of toxemias of pregnancy.

The authors' concept of the pathogenesis of hypertension is based on the theory that there is an early functional or emotional type of hypertension, in which the circulatory system is well adjusted and evidences of cardiac, renal or cerebral disorders are lacking. The only renal change seems to be a constriction of the afferent arterioles. "This may be called the neurogenic type of hypertension. Later in the course of the disease, another stage develops, in which evidences of vascular disease of the kidney, of the heart and of the arteries become evident." In this phase, the clinical picture is typical of essential hypertension. A transitional stage is also described.

Regarding the nature of the early vascular changes in essential hypertension, they believe the earliest one consists of conversion of the renal blood flow from a pulsatile to a continuous type of flow, resulting in the liberation of an enzymatic protein, renin. This, in turn, is responsible for the vasoconstriction of essential hypertension.

The proper approach to the diagnosis is taken up in a clear and simple manner. Special tests of renal function are briefly described, but the most useful ones are taken up in much greater detail. The tests recommended as most practical are (1) measurement of proteinuria, (2) counts of the urinary sediment, (3) determination of urinary concentrating power and (4) determination of urea clearance.

A study of congestive heart failure, its cause, its course and its treatment, is excellently presented and is one of the highlights of the book.

In the discussion of treatment, thiocyanate is given first place. Kidney extract and vitamin A are discussed. Treatment by surgical measures is considered, and the effects of nephrectomy on hypertensive persons is given particular notice.

The book is written in a characteristic and easy style. Altogether, it is an interesting as well as a useful and authoritative monograph on the subject of arterial hypertension.

**Penicillin and Other Antibiotic Agents** By Wallace E. Herrell, M.D. Price, \$5 Pp 348, with 45 illustrations Philadelphia W. B. Saunders Company, 1945

With a new and rapidly moving subject, it is always a question at what point one is justified in summarizing current knowledge in book form. Dr. Herrell's monograph will always be a landmark in the history of antibiotics, if for no other reason than for the excellent chapters dealing with the discovery and development of these substances, the analysis of the literature and the classification of priorities. The general physician will perhaps be most interested in the discussions of technic of preparation and administration of penicillin and of the results of treatment in various conditions. The material is extensive and well presented, although much will have to be revised in the light of future (and indeed current) work, especially the matter of time-dose relation. The reviewer feels that the continuous intravenous method of administration will, except in rare instances, be replaced by intermittent intramuscular injections or by some other more effective method. It seems also that some of the doses recommended for severe sepsis are rather small. Little is said about bacterial endocarditis, and that not too encouraging, although good results are being reported now with large doses of penicillin. Finally, the discussion of syphilis will require much extension and amplification after more cases have been followed for a few years. The book is admirably printed and illustrated, and the bibliographies are thorough. The final chapters on antibiotics other than penicillin, such as tyrothricin, will be of great value in orienting the physician in a complicated subject.

**Microbial Antagonisms and Antibiotic Substances**

By Selman A. Waksman, Professor of Microbiology, Rutgers University, and Microbiologist, New Jersey Agricultural Experiment Station. Price, \$3.75 New York Commonwealth Fund, 1945

Years of study and research in microbiology resulting in an intimate understanding of the subject have prepared the author to write this opportune book. Scientists have been aware of the interrelations of microorganisms for many years, recently an awakening to the possibilities of the practical application of these antagonistic relations has decidedly accelerated interest and investigation. The book describes and discusses the teeming microscopic plant and animal population of soil, water basins and human and animal wastes. It treats of their complicated interrelations, especially the antagonistic, the mechanisms of these reactions and the antibiotic substances produced and the utilization of antagonistic microorganisms in the control of disease in human beings, animals and plants. Since more detailed studies have been made on the production, nature and utilization of penicillin, it is natural that special attention is focused on this agent, though the many

substances possessing bacteriostatic and fungistatic properties are given due consideration. The author has successfully accomplished the difficult portrayal of a rapidly moving scene.

**Trauma in Internal Diseases** By Rudolf A. Stern, M.D., assistant attending physician, City Hospital, New York. Price, \$6.75. Pp. xxiv + 575. New York: Grune & Stratton, Inc., 1945.

This book has an interesting history. There was printed in 1899 in Breslau a volume called "Ueber traumatische Entstehung innerer Krankheiten." Its author was Dr. Richard Stern, and it was a pioneer work in the field of traumatic medicine. It achieved success, a second edition appeared in 1907 and a third edition in 1929. The third edition, however, was pretty much a new book under an old title, put together by Rudolf Stern, who was the son of the original author.

This book might be termed the first American edition of Dr. Rudolf Stern's book, or possibly the fourth edition of his father's, for it is clearly modeled on the latest German edition, and much of it is a translation. By way of rejuvenation, certain new features have been added, and the bibliography has been brought up to date. On the whole, it gives a readable account of the European viewpoint toward trauma in medicine.

**Biological Symposia, Volume XI, Aging and Degenerative Diseases** Edited by Robert A. Moore. Price, \$3. Pp. 242. Lancaster, Pa.: The Jacques Cattell Press, 1945.

This is the age of symposiums, conferences and panels, and, according to the preface, "This volume contains the papers presented at a symposium in St. Louis, March 24th and 25th, 1944, under the joint sponsorship of the Research Unit of the St. Louis City Infirmary and the Washington University School of Medicine."

The papers all deal with some phase of the process of aging, but they make no claim to a systematic coverage of the subject, nor do they show any particular correlation. Some are reflective and semiphilosophic—meditations, if you will, *de senectute*, others report concrete results of experimental work, such as the interesting contribution of Saxton on nutrition and growth and their influence on longevity in rats. The volume is well printed and illustrated. There is no index.

**Military Medical Manuals—Manual of Clinical Mycology** Prepared under the auspices of the Division of Medical Sciences of the National Research Council. Flexible cloth. Price, \$3.50. Pp. 348, with 148 illustrations. Philadelphia: W. B. Saunders Company, 1944.

This book, like its predecessors, is a compact, readable and authoritative work on a subject that is not too well known. The subject is adequately dealt with from the bacteriologic, from the dermatologic and from the medical standpoint. Even surgeons might read the book with profit. It is remarkable how much information concerning molds and yeasts has been packed into this small space. There is a section dealing with the

proper components of the various lotions, ointments and paints that may be prescribed in the treatment of these infections.

The book should be popular.

**The Examination of Reflexes** By Robert Wartenberg, M.D. Price, \$2.50. Pp. 222, with 6 diagrams. Chicago: The Year Book Publishers, Inc., 1945.

This concise little book lists and describes the methods of eliciting the innumerable reflexes used in clinical practice, discusses their significance and critically reviews the literature. The four hundred and sixty-five articles in the literature to which reference is made give an idea of the comprehensiveness of this monograph, which will be invaluable to the neurologist and the internist. The author, because of his original work in the field, seems specially qualified to discuss the subject.

**Poet Physicians, An Anthology of Medical Poetry Written by Physicians** Compiled by Mary Lou McDonough. Price, \$5. Pp. 210. Springfield, Ill.: Charles C. Thomas, Publisher, 1945.

In this anthology of medical poetry written by physicians, some of the poems are good, some indifferent and some bad, but such variations in quality would be expected in any anthology. The good poems outnumber the poor, and some of the former have become almost classic in our poetic literature. The poems are numerous. It is surprising how prolific have been the doctors who are poets. Adding to the value of this anthology is a short sketch of the life of the authors whose poems are published and whose dates range from 699 A.D. to the present time.

## News and Comment

### GENERAL NEWS

#### MISSISSIPPI VALLEY MEDICAL SOCIETY

The Eleventh Annual Meeting of the Mississippi Valley Medical Society will be held Sept. 25 to 27, 1946, at the Hotel Jefferson, St. Louis.

The Mississippi Valley Medical Society is resuming its annual Essay Contest and in 1946 will offer a cash prize of \$100, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association and residents of the United States. Contributions must not exceed 5,000 words, must be type-written in English in manuscript form, and five copies must be submitted not later than May 1, 1946. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Ill.

## ACUTE MYOCARDITIS IN MUMPS (EPIDEMIC PAROTITIS)

COMMANDER DAVID H ROSENBERG (MC), USNR

Mumps (epidemic parotitis) is generally regarded today as an acute systemic disease of virus origin, having a special predilection for the parotid glands. Among the complications most familiar to the physician are acute orchitis, pancreatitis, meningitis and meningoencephalitis. Cardiac involvement has been considered rare and when observed has been described as either acute pericarditis or acute endocarditis. That the virus of mumps may also produce myocarditis was originally suspected by Pujol<sup>1</sup> and by Barbato<sup>2</sup> from their clinical observations, but no satisfactory evidence to support their contention was presented. Later, Manca<sup>3</sup> reported the histologic changes in an instance of acute interstitial fibrinous myocarditis which occurred in a fatal case of mumps. He regarded this as a characteristic reaction to the mumps virus.

In January 1943, I had the unique opportunity of observing an instance of complete heart block in a patient convalescing from epidemic parotitis. From the electrocardiographic changes a diagnosis of acute myocarditis was made, and, in the absence of any other etiologic agent, the disease was ascribed to the virus of mumps. The following report is a brief summary of the case.

CASE 1—A C S, a white sailor aged 20 years, was admitted to the hospital on Jan 18, 1943, complaining of pain in and swelling of the right side of the face for two days. The past history was noncontributory. Physical examination revealed swelling and tenderness of the right parotid gland, with inflammation of the orifice of Stensen's duct. No other abnormal conditions were observed.

The patient's course was uneventful until the fifteenth day of illness, when he complained of constant retrosternal pain and of dizziness on arising. Examination at that time revealed no abnormalities save for a pulse rate of 35 per minute. The temperature and the respiratory rate were normal. The blood pressure was 110

systolic and 80 diastolic. The electrocardiogram taken on the same day showed evidence of complete auriculoventricular dissociation (fig 1A). The auricular rate was 104 and the ventricular rate 35 per minute. The P waves were not fixed in the ventricular cycle, they were slightly notched in lead II and inverted in lead CF<sub>4</sub>. The T waves were all upright. The blood count was normal except for a leukocyte count of 12,800 per cubic millimeter.

The sedimentation rate was 22 mm in one hour (Cutler method). Urinalysis showed nothing abnormal. On the following day the ventricular rate was 62 per minute and the rhythm was irregular, with frequent dropped beats. The electrocardiogram (fig 1B) disclosed second degree auriculoventricular block with the Wenckebach phenomenon and dropped beats. The auricular rate was 70 and the ventricular rate 62 per minute. The P-R interval ranged from 0.22 to 0.44 second. The symptoms gradually subsided in three days, but a harsh systolic murmur became audible at the mitral area. Eight days after the onset of the angina, the electrocardiogram (fig 1C) was within normal limits, the P-R interval being 0.16 second. The P waves remained notched in lead II and tiny and inverted in lead CF<sub>4</sub>. The sedimentation rate and the leukocyte count returned to normal. The systolic murmur diminished in intensity, and at the time that patient was discharged from the hospital it was soft and heard only at the apex when the patient was in the recumbent position.

Early in 1944, another patient was observed who during the course of mumps manifested electrocardiographic evidence of partial heart block which progressed to complete heart block and ultimately returned to normal. Again, the diagnosis of acute myocarditis secondary to the virus of mumps was made. Following is a résumé of this case.

CASE 2—J B B, a white sailor aged 20 years, was admitted to the hospital on Feb 21, 1944, complaining of pain in and swelling of the right side of the face for two days. The past history was noncontributory. Physical examination revealed swelling and tenderness of the right parotid gland. No other abnormal findings were elicited.

His course was uneventful until the seventh day of illness, when palpitation and precordial pain developed. Examination disclosed an apical rate of 28 per minute. No other abnormalities were noted. The temperature was 101 F (rectal) and the respiratory rate 16 per minute. The blood pressure was 110 systolic and 52 diastolic. The electrocardiogram taken on the same day showed second degree auriculoventricular block (3:1), with only one out of three auricular impulses being conducted to the ventricles (fig 2A). The auricular rate was 99 and the ventricular rate 33 per minute. The P waves were fixed in the ventricular cycle. The P-R interval of the conducted sinus impulses was 0.28

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

1 Pujol, M. Oreillons et myocardite, *Arch de med et pharm mil* 69 527, 1918.

2 Barbato, M. Un caso di parotite epidemica con complicazioni viscerali multiple, ed esito letale, *Riforma med* 41 1109 (Nov 23) 1925.

3 Manca, C. Miocardite da parotite epidemica, *Arch ital di anat e istol pat* 3 707 (July-Aug) 1932.

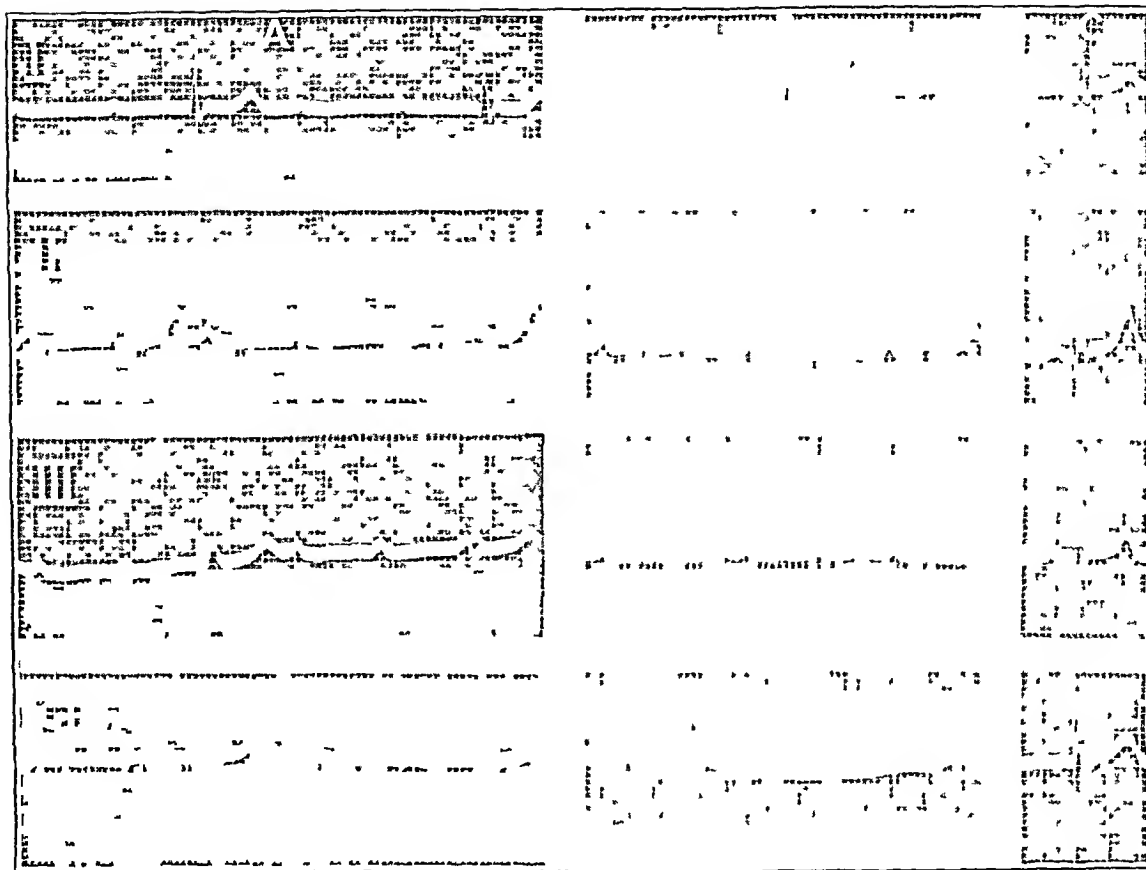


Fig 1—Electrocardiograms taken on A C S (case 1) on the fifteenth (*A*), sixteenth (*B*) and twenty-second (*C*) days of illness *A* shows the characteristic findings of complete auriculoventricular dissociation. In *B*, evidence of improvement is demonstrable in the finding of second degree auriculoventricular block with dropped beats and the Wenckebach phenomenon. In *C*, the electrocardiogram has returned to normal (see text for details).

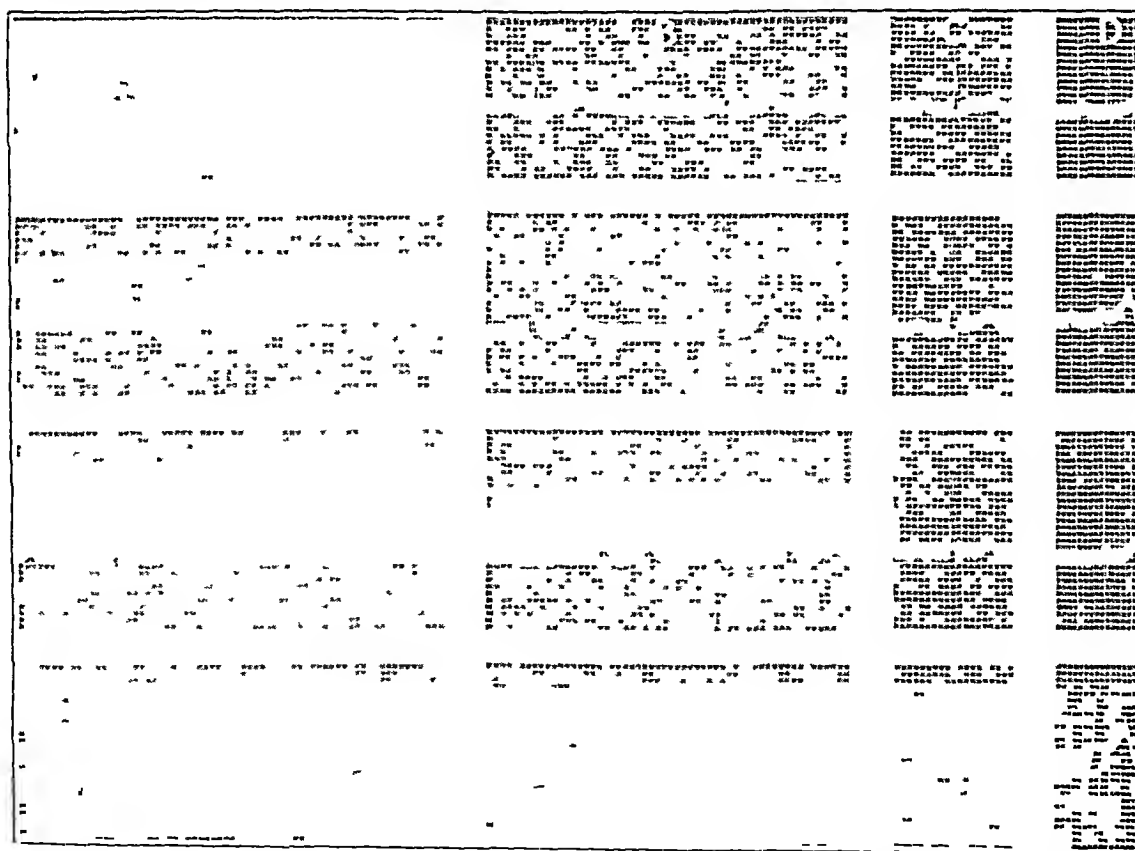


Fig 2—Electrocardiograms taken on J B B (case 2) on the seventh (*A*), tenth (*B*), twenty-first (*C*) and eighty-first (*D*) days of illness. In *A*, the electrocardiogram discloses second degree auriculoventricular block (3:1) with dropped beats. The P-R interval of the conducted sinus impulses is 0.28 second. In *B*, the block has increased to complete auriculoventricular dissociation. *C* shows only first degree auriculoventricular block, with prolongation of the P-R interval to 0.23 second, indicating considerable improvement. In *D*, the electrocardiogram has reverted to normal (see text for details).

second The P waves were peaked in lead II and small and inverted in lead CF<sub>4</sub>. The T waves were tall, notched and varied in contour because of superimposed P waves. The sedimentation rate was 33 mm in one hour. The blood count was normal except for a leukocyte count of 11,400 per cubic millimeter. Urinalysis revealed nothing abnormal. Examination three days later revealed variations in the intensity and quality of the heart tones, suggesting complete heart block. The electrocardiogram on that day showed complete auriculoventricular block, with an auricular rate of 91 and a ventricular rate of 52 per minute (fig 2B). There was no fixed relation between the P waves and the QRST complexes. The P waves varied in contour (wandering pacemaker). The temperature remained elevated for five days, and palpitation continued for sixteen days. The electrocardiogram taken on the fifteenth day of this complication (fig 2C) revealed only first degree auriculoventricular block, with a P-R interval of 0.23 second (normal, 0.12 to 0.21 second). All auricular beats were conducted, and the auricular and ventricular rates were 68 per minute. These electrocardiographic abnormalities remained until the seventeenth day of the complication, when the electrocardiogram was normal (fig 2D). The patient was discharged from the hospital six weeks later feeling well. At no time were any cardiac murmurs detectable.

A review of the literature revealed no references to any similar observations. Hence, a study of the electrocardiographic findings in epidemic parotitis was undertaken as an approach to the determination of the incidence, course and prognostic significance of acute myocarditis due to the virus of mumps.

#### MATERIAL AND METHODS

Electrocardiographic tracings were taken on a consecutive series of 104 adults with mumps who were admitted to a large naval hospital during the height of an epidemic early in 1944. All except 2 patients were men. The ages ranged from 17 to 40 years, the average for the group being 21 years. Standard limb leads and chest lead CF<sub>4</sub> were used in all cases. For 46 of these patients, serial electrocardiograms were made at intervals of two to four days. This study was correlated with determinations of the sedimentation rate (Cutler method)<sup>4</sup> and with blood counts. In addition, a careful search was made for clinical evidence of cardiac involvement. The patients showing electrocardiographic abnormalities were studied further to exclude the possibility of coexistent etiologic factors.

#### RESULTS

In 16 of the 104 patients studied, significant electrocardiographic evidence of myocardial involvement was found (15.4 per cent). In these no other concomitant disease or infection was recognizable. Electrocardiographic abnormalities were observed in 3 other patients of this series, but in 1 of these the electrocardiographic changes were characteristic of the Wolff-

Parkinson-White syndrome, currently believed to be a congenital anomaly, in another, the abnormality was constant and could be attributed to a congenital deformity of the thoracic wall, in the third patient, there was a history of migratory pains in the joints for four months prior to the onset of mumps and physical signs of mitral stenosis, thus indicating the likelihood of rheumatic carditis. These 3 cases have therefore been excluded from consideration.

An analysis of the electrocardiographic abnormalities<sup>5</sup> in the group of 16 patients revealed the following facts<sup>6</sup>. In 4 patients the P waves became diphasic or inverted in one or more leads (fig 3). Prolongation of the P-R interval was found in 2 instances (fig 4). In 1 person, the QRS complex in CF<sub>4</sub> became inverted, and in another the voltage in the limb leads decreased. Two patients showed significant elevation of the S-T segments in CF<sub>4</sub>, and in 1 of these the S-T segment was bowed upward. In 1 subject, the S-T segment became depressed beyond normal in leads II and III. Changes in the T waves were observed in all the 16 patients, and in 2 of these they were noted in two or more leads (figs 4 and 5). The T waves became tiny, diphasic or inverted, and by means of serial electrocardiographic studies the evolutionary stages in the development of T wave inversion could be demonstrated. Alterations of the T wave occurred with essentially the same frequency in each of the four leads. In 14 out of the 16 patients, more than one abnormality was found. In the other 2, significant changes in the T wave were found in either lead I or lead II. No specific electrocardiographic pattern was recognizable in this study.

It is noteworthy that in all but 1 patient the electrocardiographic abnormalities were observed between the fifth and the tenth day of illness, and in the majority of these they were present on the eighth or the ninth day. In the other subject, an abnormal tracing was not found until the twentieth day of illness. In 14 patients, the electrocardiographic changes returned to normal in two to thirty-five days. In most of these instances, however, the curves were normal in four to eight days. In the remaining 2 patients, although electrocardiographic evidence of progressive improvement was observed early in the course of this complication, minor residual

<sup>5</sup> Rosenberg, D. H. The Electrocardiographic Changes in Epidemic Parotitis (Mumps), *Proc Soc Exper Biol & Med* 58:9 (Jan) 1945.

<sup>6</sup> Dr Louis N. Katz, Director of Cardiovascular Research, Michael Reese Hospital, Chicago, reviewed the electrocardiographic tracings and concurred in the findings and their interpretation.

<sup>4</sup> Cutler, J. A Graphic Presentation of Blood Sedimentation Test. A Study in Pulmonary Tuberculosis, *Am J M Sc* 171:882 (June) 1926.

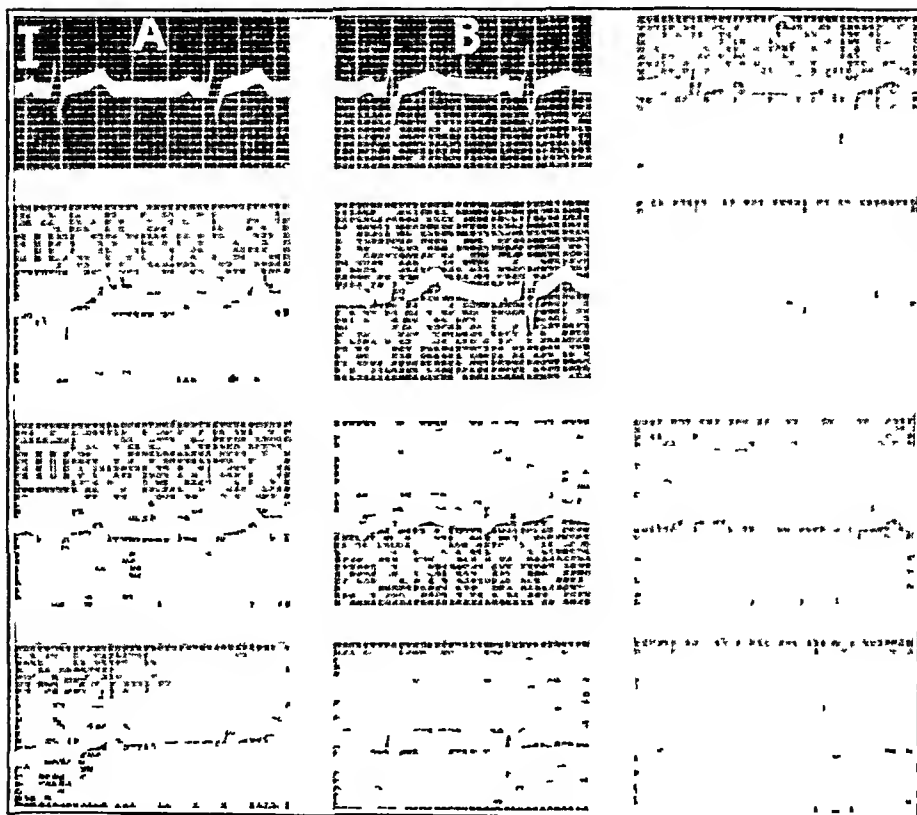


Fig 3—Electrocardiograms taken on R J P on the fifth (*A*), ninth (*B*) and thirteenth (*C*) days of illness, demonstrating changes in the P waves and the T waves. In *A*, the electrocardiogram is normal. In *B*, the P waves have become diphasic in lead II, and sharply inverted in lead III. The T waves are of lower amplitude in leads I, II and III and are inverted in lead  $CF_4$ . In *C*, the electrocardiogram is again normal.

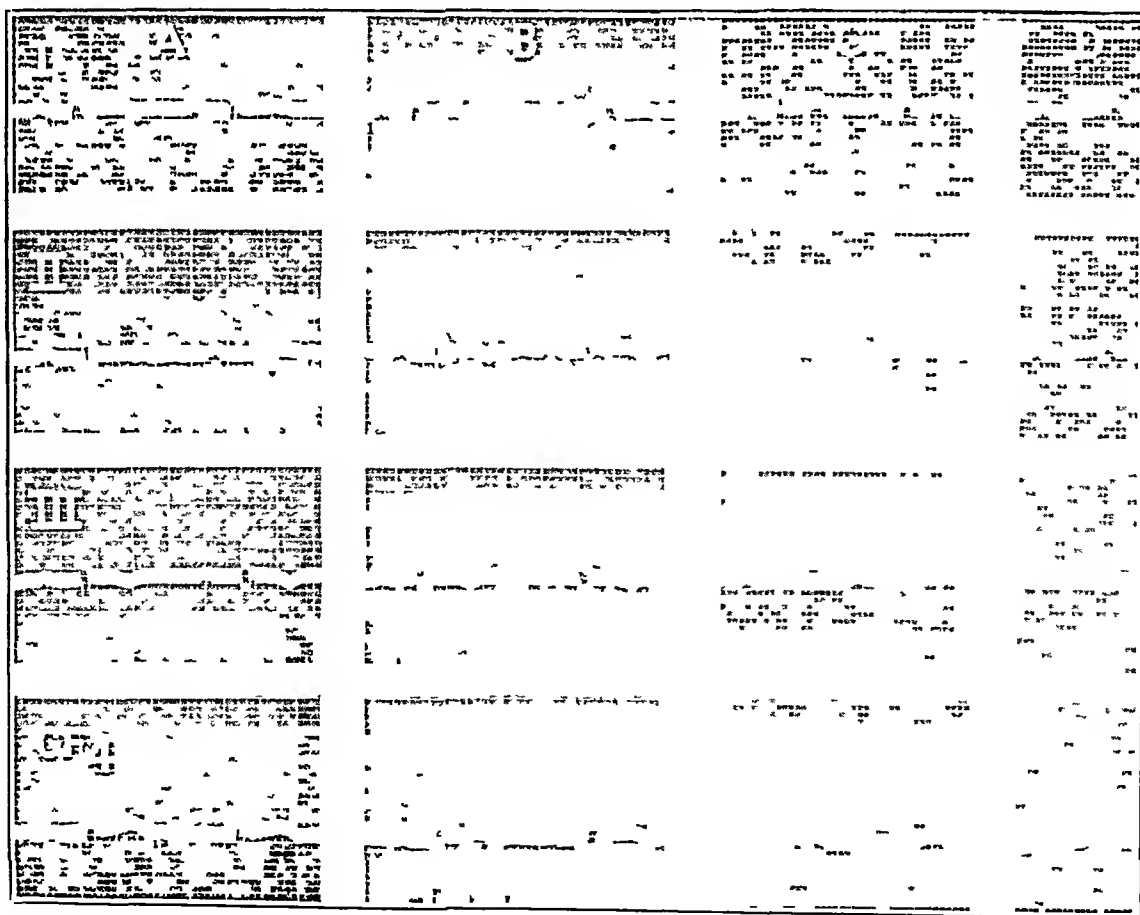


Fig 4—Electrocardiograms taken on J L C (case 47) on the seventh (*A*), fourteenth (*B*), thirty-seventh (*C*) and ninety-third (*D*) days of illness, showing prolongation of the P-R interval and T wave changes. In *A*, the P-R interval is prolonged to 0.24 to 0.27 second, the T waves are of low amplitude in lead I and notched in lead II. In *B*, the P-R interval is 0.22 second, the T waves have become inverted in leads I and II and tiny in lead  $CF_4$ . In *C*, the P-R interval is 0.22 second, the T waves are now upright in leads I and II and taller in lead  $CF_4$ . In *D*, the electrocardiogram has returned to normal.

changes persisted for three months and five months respectively, ultimately reverting to normal

Precordial pain, either alone or with dyspnea and palpitation, developed in 4 of the 16 patients. In 1 of these, dull precordial pain appeared on the third day of illness and recurred for sixteen days. A soft blowing systolic murmur became audible at the mitral area in all positions and persisted for two months. Two days after the onset of precordial pain, the P waves were inverted in leads II and III, the S-T segment in lead  $CF_4$  was elevated and the T waves in lead III were diphasic. Within thirty-five days the P and T deflections became upright and the S-T segment

parotitis. However, the electrocardiograms were abnormal on the seventh and ninth days of illness respectively. In patient 47, the P-R interval was prolonged and the T waves became inverted in leads I and II (fig 4). In patient 72, the T waves became tiny in lead I and inverted in leads II, III and  $CF_4$  (fig 5), a soft blowing systolic murmur was audible at the mitral area on the twenty-first day of illness and did not disappear until two months later. When the electrocardiographic changes in these 2 patients were correlated with the time of onset of the cardiac symptoms, it was disclosed that normal electrocardiographic findings had been present for only one to two weeks prior to the resumption of activity in

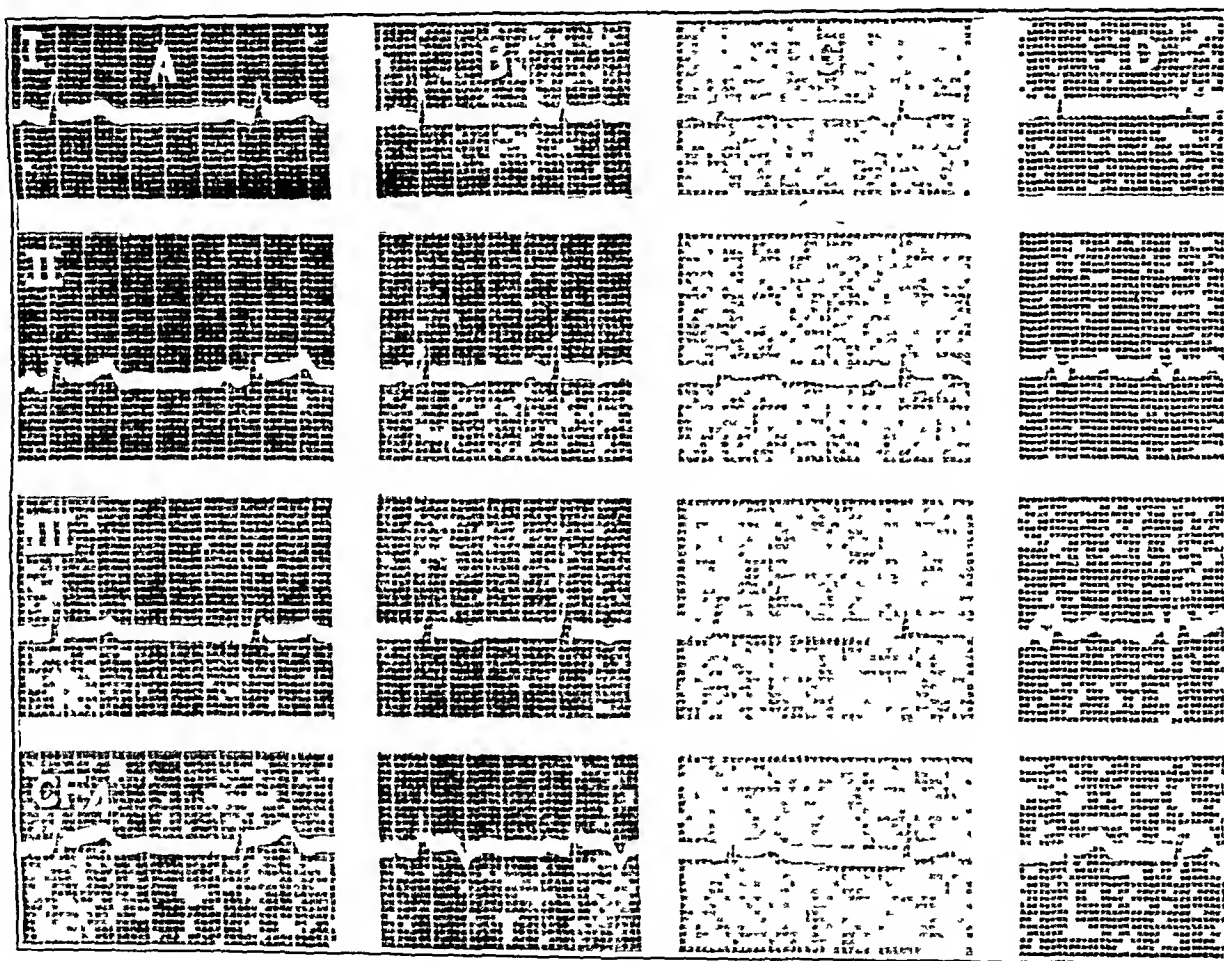


Fig 5—Electrocardiograms taken on J. T. A (case 72) on the fifth (A), ninth (B), thirteenth (C) and thirty-second (D) days of illness, demonstrating changes in the T waves. In A, the electrocardiogram is essentially normal. In B, the T waves have become tiny in lead I and inverted in leads II, III and  $CF_4$ . In C, the T waves are upright in leads II, III and  $CF_4$  but are of low amplitude in leads I, II and III. In D, the electrocardiogram is again normal except for low amplitude T waves in lead I.

was normal. In another subject, constricting precordial pain radiating to the left shoulder and arm was noted on the second day of illness. It was accompanied with dyspnea and palpitation and lasted for nine days. Seven days after the onset of these symptoms the T wave in lead I became diphasic and small and returned to normal four days later. In the other 2 patients (cases 47 and 72) mild recurrent precordial pain, palpitation and fatigue developed three months and six weeks respectively after the onset of

the ward. Longer periods of rest and decreased activity were considered advisable and were followed by a gradual abatement of symptoms. None of the other patients in this study revealed either subjective or objective evidence of any cardiac abnormality except for the aforementioned patient with rheumatic mitral stenosis.

The sedimentation rate was elevated in only 5 of the 16 patients, the maximum reading being 22 mm in one hour. A slight leukocytosis (11,000 to 11,600 leukocytes per cubic millimeter)

was found in 3 patients, and in another the leukocyte count was 14,000 per cubic millimeter. In 7 of the 16 patients acute orchitis developed. It was in 4 of these patients that the leukocytosis appeared and in 3 the sedimentation rate was elevated.

#### COMMENT

The electrocardiographic conditions observed in 16 of the 104 patients studied would seem to indicate that, contrary to the prevailing literature, myocardial involvement is not a rare event during the course of epidemic parotitis in adults. It should be emphasized that this study was conducted during the peak of an epidemic and that the incidence may be lower during the declining period or in sporadic cases, when the infection is less virulent. Since the completion of this work, attention was directed to Wendkos and Noll's<sup>7</sup> report of a case with prolonged P-R interval and T wave changes occurring among a group of 15 soldiers convalescing from mumps. In their paper, there is no indication that serial electrocardiograms were taken for the 14 patients with normal electrocardiograms or in what stage of recovery the electrocardiographic study was made.

Electrocardiographic evidence of myocardial involvement, when present, appears as a rule between the fifth and tenth days of illness and in this respect is similar to acute orchitis and meningoencephalitis. It is usually transitory in nature, lasting four to eight days in the majority of cases, although occasionally remaining for as long as three to five months. In only 4 patients of this series and in the 2 isolated instances herein recorded did cardiac symptoms become manifest, and in 3 of these a soft blowing systolic murmur appeared. Inasmuch as these murmurs disappeared, they were considered as functional in origin, and no definite diagnostic significance could be attached to them. The presence of a slow or irregular pulse was not necessarily indicative of myocardial involvement, for in a number of such instances the electrocardiograms showed no deviations from normal. It follows, therefore, that the recognition of this complication resides chiefly, if not exclusively, in the results of an electrocardiographic study and that in the majority of cases the cardiac lesion remains at a subclinical level. No sequelae were observed in this group of patients, although convalescence was protracted in 2 instances. Pujol,<sup>8</sup> however, reported 3 soldiers with dyspnea, palpitation, tachycardia and/or precordial pain following an

attack of mumps, and I have been informed<sup>9</sup> of other instances in adults with similar symptoms, but without pain, which persisted for several weeks. It is likely that at least in some of my patients the good results may be attributed to the regimen of periodic rest and decreased activity, which was observed for two to three weeks after the electrocardiograms became normal.

The nature of the histopathologic changes in the myocardium is conjectural. Whether or not they represent an acute interstitial fibrinous myocarditis with infiltration of polymorphonuclear leukocytes, as in Manca's case, must be determined by further study. The likelihood of pursuing this problem in human subjects is remote, inasmuch as epidemic mumps is rarely fatal. Information may, however, evolve from observations on experimental animals. From the clinical course and the character of the electrocardiographic observations, the assumption may be drawn that the myocardial changes are usually mild and that they are reversible. For an occasional patient with more extensive involvement, such as those with heart block, failure to recognize this complication may jeopardize the prospects of complete recovery or delay restitution.

The results of this study are provocative of certain implications and considerations which are of both academic and clinical importance. There are authenticated instances of acute orchitis, meningitis and meningoencephalitis due to the virus of mumps which antedate the appearance of parotitis, in some, the parotitis is so slight as to escape recognition. So, too, is it possible to find electrocardiographic evidence of myocardial involvement due to the mumps virus without clinical signs of parotitis, and in such cases, particularly if accompanied with arthralgia, the presumptive diagnosis of rheumatic fever would seem tenable. Indeed, there is a striking similarity between the electrocardiographic abnormalities in mumps and those which were observed<sup>9</sup> in a large series of patients at a naval hospital. It is pertinent to add that other acute infections which are prevalent in epidemic form when the incidence of rheumatic fever is at its peak, such as pneumonia, diphtheria and German measles, were also found with electrocardiographic abnormalities, including prolonged P-R interval. These observations considered collectively cast further doubt on the specificity of the delayed conduction time and suggest that perhaps too much emphasis is being attached to the significance of this finding in the differential diag-

<sup>8</sup> Personal communication to the author.

<sup>9</sup> Rosenberg, D. H. Rheumatic Fever in the Adult, paper read at the First Annual Clinical Conference of the Chicago Medical Society, March 1944.

<sup>7</sup> Wendkos, M. H., and Noll, J., Jr. Myocarditis Caused by Epidemic Parotitis, *Am Heart J* 27:414 (March) 1944.

nosis of rheumatic fever. There are doubtless many cases both in the armed forces and among civilians which are labeled as instances of rheumatic fever without sufficient justification other than the presence of arthralgia, unexplained fever or prolonged P-R interval. In view of the growing interest in rheumatic fever and the institution of programs of study dealing with its incidence, prevention and care, there is an urgent need for a more precise definition of rheumatic fever as well as for more specific diagnostic criteria.

It may be argued that perhaps streptococcal infections of the upper respiratory tract (subclinical) or rheumatic fever coexisted in my patients with mumps and that they were responsible for the myocardial changes. Obviously, one cannot settle this point conclusively. It should be pointed out, however, that except for case 1 all the patients with electrocardiographic abnormalities had been participating in the program of continuous mass prophylaxis (sulfadiazine, 1 Gm daily) then in effect at a large naval training center and that the incidence of infections of the respiratory tract and of rheumatic fever was at the lowest level at the time of this study.

Finally, the observations recorded in this paper present further evidence to substantiate the belief that epidemic parotitis is a generalized infection and that any acute infectious disease, bacterial or viral in origin, is capable of affecting

the heart, however infrequent or minimal this may be. As a corollary to this, the cardiac factor may contribute to the causation of some of the symptoms frequently observed during convalescence.

#### SUMMARY AND CONCLUSIONS

Two isolated cases of mumps complicated by acute myocarditis with electrocardiographic evidence of complete heart block are reported.

In a subsequent study of 104 consecutive cases of mumps in adults, electrocardiographic evidence of myocardial involvement was found in 16 instances (15.4 per cent). The variations in the electrocardiographic observations are presented.

Mumps myocarditis appears as a rule between the fifth and tenth days of illness and is usually mild and transitory. In the majority of instances, it follows a subclinical course and is recognizable chiefly, if not exclusively, by electrocardiographic studies.

Precordial pain, dyspnea and/or palpitation appeared in 4 cases of this series and in the 2 isolated cases.

The implications and the importance of these observations are discussed, particularly as they pertain to the diagnosis of rheumatic fever.

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# PNEUMOTHORAX IN YOUNG ADULT MALES

## DESCRIPTIVE STATISTICS IN ONE HUNDRED AND TWENTY-SIX CASES

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Spontaneous pneumothorax has been the subject of numerous reports in the literature. With relatively few exceptions,<sup>1</sup> most reports have been concerned with small groups of cases or with isolated patients who have presented unusual features or complications. The reports of larger numbers of cases have usually been drawn from clinics or sanatoriums dealing with tuberculous patients. Reports of this type necessarily must be colored by the relation of pulmonary tuberculosis and spontaneous pneumothorax, consequently, the results are biased in one direction.

The following report is based on a study of 126 patients with 129 episodes of spontaneous pneumothorax observed among military personnel in the Army Air Forces Training Command. Since all military personnel have a roentgenogram of the chest made prior to entrance into the service and since many have roentgenograms made after entering on active duty, the results observed in this group are biased in the opposite direction, namely, away from tuberculosis.

*Source of Material for Study*—Certain hospitals in the Command were requested to furnish clinical records and pertinent roentgenograms from all cases of spontaneous pneumothorax in their files. The material was assembled and studied in the Office of the Surgeon of the Army Air Forces Training Command.

1 (a) Ornstein, G. G., and Lercher, L. Spontaneous Pneumothorax in Apparently Healthy Individuals, *Quart Bull Sea View Hosp* 7 149-187 (April) 1942. (b) Kjaergaard, H. Spontaneous Pneumothorax in Apparently Healthy, *Acta med. Scandinav*, 1932, supp 43, pp 1-159 and 1-93, cited by Blackford, S. D. Spontaneous Pneumothorax in College Students, *J A M A* 113 737-739 (Aug 26) 1939. (c) Olbrechts, E. Le pneumothorax spontané "idiopathique" Bérnin, *Ann de med* 27 429-483 (May) 1930. (d) Norris, J. L. Spontaneous Pneumothorax, Industrial Experience with 25 Cases, *New York State J Med* 40 504-506 (April 1) 1940. (e) Bassel, P. M. Spontaneous Pneumothorax, *Texas State J Med* 32 696-700 (Feb) 1937. (f) Kirshner, J. J. Spontaneous Pneumothorax, *Am J M Sc* 196 704-709 (Nov) 1938. (g) Blackford, D. Spontaneous Pneumothorax in College Students, *J A M A* 113 737-739 (Aug 26) 1939.

The 126 patients reported on by no means represent all the cases of pneumothorax that have been observed. Some records could not be used because of incompleteness, or the complete records had been forwarded to Veterans' facilities or to general hospitals at the time the patients were transferred. However, no other selective principle was used in settling on the population of the 126 cases included in this study.

*Results*—So far as possible the data have been assembled and presented in the form of tabulations, both for ease of discussion and reference and for use in comparing or combining with other data that may be reported by others. In connection with each tabulation is presented a comment on the significance of pertinent features or unusual aspects of the data.

*General Considerations*—There were 126 male patients with 129 episodes of pneumothorax (1 patient had 1 recurrence and 1 patient had 2 recurrences during the period covered by this survey). There were 5 ground officers, 80 non-flying enlisted men, 4 pilots and 1 bombardier, 1 navigator, 3 aerial gunners, 2 student flying officers and 30 aviation cadets. Ages ranged from 18 to 41 years, averaged 24.8 years, with a standard deviation of 5.6 years. There were no immediate fatalities. The number of fatalities among those transferred (10 patients) beyond the jurisdiction of this command is unknown.

*Special Considerations*—It has been taught that the onset of spontaneous pneumothorax is usually sudden and is associated with rather pronounced symptoms of dyspnea, pain in the chest, pallor and evidences of cardiovascular embarrassment even to the point of shock. In an appreciable portion of these patients the onset was gradual (table 1). In another appreciable portion the initial symptoms were either nonexistent (ranging from vague discomfort in the chest to absolutely no symptoms) or mild in character. The difference between those exhibiting no symptoms or only mild ones (63.5 per cent) and those exhibiting moderate and severe symptoms (36.5 per cent) is statistically significant.

It is possible that the generally high state of physical fitness of the men contributed to the mildness of the symptoms. There was no association between the severity of the reported symptoms at the onset of the attack and the degree of pulmonary collapse.

TABLE 1—Onset and Initial Symptoms of the Attack (One Hundred and Twenty-Nine Attacks)

Onset	Number	Per Cent of Number	Per Cent of Number with Unknown Onset Eliminated
Gradual	23	17.8	20.2
Sudden	90	69.8	79.8
Unknown or unstated	16	12.4	
Total	129	100.0	100.0

Initial symptoms	Number	Per Cent of Number	Per Cent of Number with Unstated Symptoms Eliminated
None	8	6.2	6.8
Mild	67	52.0	56.7
Moderate	6	4.7	5.1
Severe	37	28.6	31.4
Unstated	11	8.5	
Total	129	100.0	100.0

In table 2 it is significant to note that in 76 patients there was nothing in the past medical history that had any reasonable association with the onset of spontaneous pneumothorax. In addition, 18 patients had infections of the upper respiratory tract, many of which were

TABLE 2—Significant Past Medical History up to Onset (One Hundred and Twenty-Nine Attacks)

	Number	Per Cent
None contributory (4 found on routine roentgenographic examination)	76	59.0
Concomitant infection of the upper respiratory tract (6 without cough, 13 with cough)	18	14.0
History of previous pleural pain	6	4.6
Concomitant acute pleuritis	3	2.3
Previous empyema	1	0.8
Chronic pulmonary emphysema	1	0.8
Concomitant pneumonia (1 lobar, 1 broncho pneumonia, 1 virus)	3	2.3
Exposed to or studied for tuberculosis	5	3.9
Inactive pulmonary tuberculosis	1	0.8
Indirect trauma (struck on face)	1	0.8
Possible previous pneumonia	3	2.3
Previous pneumothorax	8	6.2
Possibly associated with "flight" in low pressure chamber	3	2.3
Total	129	100.0

mild. Although 13 had an infection of the upper respiratory tract associated with cough, in only 1 instance did the pneumothorax occur during a period of coughing.

Those patients who had a history of previous pneumothorax will be commented on separately, since they are of themselves an interesting group. The remaining categories are too scattered and do not constitute sufficiently large groups for separate consideration.

Three patients, 2 of whom gave vague histories dating from a low pressure chamber "flight" one month prior to the onset of the pneumothorax and 1 in whom the onset of pneumothorax occurred during a "flight," are included only to make a point. When one considers the large number of "man flights" made daily in low pressure chambers in this Command entirely unassociated with pneumothorax, these 3 instances seem extraordinarily unimportant.

None of these 129 onsets occurred during aerial flight.

There have been many discussions in the past concerning the relation between physical activity and the production of pneumothorax. A division of the cases into groups according to amount of physical activity (none, mild or moderate activity and extreme activity), based on the premise that with chance factors alone operating there would be an equal distribu-

TABLE 3—Physical Activity at Onset

	Number	Per Cent of Number	Per Cent of Number with Unstated Activity Eliminated
At rest (30 in bed, 20 sitting)	50	38.8	48.6
Mild physical activity (6 leaning over, 11 standing, 20 walking, 2 climbing stairs)	39	30.2	37.8
Extreme physical activity (4 running, 8 violently exercising, 1 coughing, 1 fighting)	14	10.8	13.6
Unknown or unstated (includes 4 discovered in routine roentgenographic examination)	26	20.2	
Total	129	100.0	100.0

tion in the three categories, brings out two important features (table 3). In a significantly higher percentage (48.6 per cent) of cases than would be grouped together by chance, the onset of pneumothorax was associated with a minimum of physical activity. In a significantly lower percentage (13.6 per cent) of cases, the onset was associated with extreme physical activity.

This distribution suggests two explanations. First, the amount of physical activity has little to do with the onset of the average case of pneumothorax or, second, the cause of pneumothorax occurring at rest is quite different from the cause of that occurring during exercise.

There was no association between the amount of physical activity and either the symptoms or the degree of collapse at the onset.

It can be seen by a glance at table 4 that the valvular type of pneumothorax was an unusual occurrence in this group.

The more frequent occurrence of pneumothorax on the right side has been noted before<sup>1a</sup> In this group 59.8 per cent of the occurrences were on the right side (table 4). This difference from a chance distribution is significant at the 1 or 2 per cent level. When this group is com-

TABLE 4—Type and Side of Occurrence of Pneumothorax

Type of pneumothorax	Number	Per Cent of Number	Per Cent of Number with Unstated Side Eliminated
Closed	127		98.5
Valvular	2		1.5
Side of pneumothorax			
Right	76	59.9	59.8
Left	50	38.8	39.4
Bilateral	1	0.7	0.8
Unstated	2	1.6	

bined with the cases reported by Ornstein and Lercher<sup>1a</sup> (25 single attacks on the right side and 16 on the left) the difference between the frequency of right-sided and left-sided pneumothorax is highly significant (0.1 per cent level).

It is not apparent from these data why spontaneous pneumothorax occurs more frequently on the right side.

TABLE 5—Degree of Collapse and Rate of Reexpansion

Days to Complete Reexpansion	Group I Up to 50% Collapse, Number	Group II Greater Than 50% Collapse, Number	Both Groups, Number
0 to 10	6	1	7
11 to 20	32	1	33
21 to 30	12	4	16
31 to 40	4	12	16
41 to 50	1	5	6
51 to 60	0	8	8
61 to 70	1	1	2
71 to 80	0	2	2
81 to 90	0	0	0
91 to 100	0	3	3
101 to 110	0	0	0
111 to 120	0	1	1
Total	56 (59.5%)	38 (40.5%)	94 (100%)*
Mean in days †	19.43	48.39	31.14
Standard deviation of distribution	10.29	23.16	21.96
Standard error of mean	1.39	3.71	2.27

\* For 32 patients, not all the roentgenograms were submitted. Hence, these cases could not be included.

† The critical ratio of difference between means of groups I and II is 7.3.

The estimation of the per cent of collapse in pneumothorax is variable because of differences of method among roentgenologists and variations in technic in making roentgenograms. In compiling the data shown in table 5, these differences have been minimized as much as possible by making only two groups, namely, those with pulmonary collapse up to 50 per cent and those with collapse over 50 per cent.

These data show (a) a suggestion of a likelihood that the degree of pulmonary collapse will be less than 50 per cent and (b) a highly significant difference between the mean number of days required for complete reexpansion to take place in groups I and II. As a matter of fact, in this distribution slightly over one half of all the patients had degrees of pulmonary collapse estimated at below 33 per cent.

The cause of the pneumothorax could not be determined for the great majority of the patients, despite the fact that all the usual diagnostic measures were carried out. It is possible that the condition in a goodly portion of those patients transferred to general hospitals and veterans' facilities was tuberculous in origin (table 6).

TABLE 6—Cause (One Hundred and Twenty-Nine Attacks)

	Number
Undetermined	107
Emphysema	1
Proved pulmonary tuberculosis	1
Pneumonia	1
Pleurisy	1
Postoperative	1
Unknown because of transfer or because still in hospital	17
Total	129

For the sake of emphasis it should be stated that subpleural emphysematous blebs or visceroparietal pleural adhesions could not be demonstrated on the roentgenograms. It is possible, of course, that they might have been demonstrated by views of the thorax from other angles.

From table 7 it is evident that complications in the course of the pneumothorax were infre-

TABLE 7—Complications in the Course of Pneumothorax

Complications	Number	Per Cent
None	102	79.2
Slow absorption	3	2.3
Thoracentesis for excessive pain or dyspnea	2	1.5
Hemothorax	2	1.5
Increase in degree of pneumothorax	4	3.1
Associated injuries or other diseases	2	1.5
Pneumonia and pleurisy	4	3.1
Unstated or unknown	10	7.8
Total	129	100.0

Days of Hospitalization	
Range	4 to 135 days
Mean days	39.9 days
Standard deviation of distribution	26.6 days

quent. The average length of hospitalization (39.9 days) was determined largely by the average number of days (31.1 days) required for the air to be reabsorbed, plus additional days (average eight days) for further convalescence.

TABLE 8—Disposition of Personnel

	Number	Per Cent
Retained in military service (82 full duty, 11 limited service)	93	73.8
Certificate of disability discharge	13*	10.3
Still in hospital	7	5.6
Unknown because of transfer	10	7.9
Unstated disposition	3	2.4
Total	126	99.9

\* One was separated because of constitutional psychopathy and 1 because of nonspecific ulcerative colitis

TABLE 9—Disposition of Flying Personnel

Disposition	Number
Restored to flying after leaving hospital (1 pilot, 1 student officer, 2 aerial gunners, 1 aviation cadet)	5
Temporarily suspended from flying (1 pilot, 1 bombardier, 1 navigator, 1 aerial gunner, 1 student officer, 1 aviation cadet)	6
Grounded for 12 months (aviation cadet)	1
Indefinitely suspended (all aviation cadets)	19
Unstated disposition (1 pilot, 6 aviation cadets)	7
Still in hospital (1 pilot, 2 aviation cadets)	3
Total	41

history of previous pneumothorax (table 10). The 7 patients had a total of 11 previous episodes of pneumothorax. It is interesting that 5 of the 7 patients had recurrences on the right side. It is also noteworthy that the recurrences were not associated with unusual physical activity. There were several additional patients who gave suggestive histories of previous attacks of pain in the chest and/or dyspnea, but these could not be included in this group because of the indefiniteness of the histories. One cannot draw any conclusions from these cases on the degree of tendency of pneumothorax to recur, since the group is too small and the time period covered is too short.

## COMMENT AND SUMMARY

As noted before, this group of patients, previously screened for chronic pulmonary disease (chiefly pulmonary tuberculosis) prior to en-

TABLE 10—Recurrent Pneumothorax\*

Patient	Age	Number of Previous Attacks	Side of Previous Attack	Side of Present Attack	Degree of Collapse Present Attack (%)†	Physical Activity at Onset of Present Attack	Days to Complete Absorption
1	24	2	?	R	+50 ?	Walking	38
2	19	1	L	R	+50	Marching and counting cadence	35
3	19	2	R	R	?	?	?
4	34	2	L	L	-50	Sleeping	26
5	21	2	R	R	?	Marching	?
6	23	1	?	L	+50	Leaning over	43
7	26	1	L	R	-50	Mild physical activity	27
Total 7		11	4L 4R 3 ?	2L 5R			

\* All recurrences, except one, were within 1 to 2 years of the present attack.

† The symbol +50 indicates greater than 50 per cent collapse, -50 indicates less than 50 per cent collapse.

Of 126 persons, 93 were retained in the military service (table 8), a salvage of 73.8 per cent. Of the remaining persons, 13 were known to have been separated from the service, and possibly half of the 10 patients who were transferred to other medical facilities (usually because of troublesome complications or for administrative reasons) were also discharged for physical disability.

Of the 41 patients who were flying personnel, the disposition varied considerably (table 9). The trained personnel (pilots, bombardier, navigator and aerial gunners) and the student officers were either restored to flying directly after hospitalization or suspended from flying up to twelve months and then restored. The aviation cadets and aviation students, for the most part, were physically disqualified for further flying duty.

There were 7 patients (1 with 2 recurrences during the period covered) who gave a positive

trance on active duty, cannot be considered a general sample of the adult male population. The screening accomplished by the preservice roentgenogram of the chest largely negates the known relation between pulmonary tuberculosis and pneumothorax. However, by so doing, it brings to the fore those types of pneumothorax which for want of a better term, have been designated "spontaneous pneumothorax in healthy adults," noted by Hall<sup>2</sup> and later by Kjaergaard<sup>1b</sup>. Olbrechts<sup>1c</sup> described a similar type of pneumothorax among French army conscripts, "the pneumothorax of conscripts."

From the results obtained in this group so heavily weighted with the nontuberculous type of

2 Hall, F. de H. On Cases of Pneumothorax in Persons Apparently Healthy, *Tr. Clin. Soc., London* 20:153-161, 1886-1887, cited by Van Astrand, H. S. Idiopathic Spontaneous Pneumothorax, *Cleveland Clin. Quart.* 7:178-183 (July) 1940.

spontaneous pneumothorax some interesting observations can be made

1 Not infrequently the onset may be gradual rather than sudden

2 Initial symptoms are frequently absent (none, vague symptoms or atypical symptoms) or mild in degree

3 A positive or associative history of previous pulmonary disease is not usually found (an idiopathic pneumothorax)

4 In 85 out of 100 cases the onset of the attack occurred when the patient was at rest (48.6 per cent) or during mild physical activity (37.8 per cent)

5 The side of the pneumothorax is more frequently the right

6 The closed type of pneumothorax is most common

7 The degree of collapse is frequently less than one third, and on the average the air can be expected to be absorbed in about twenty days in those who have less than 50 per cent pulmonary collapse

8 A search for the causative factor in these cases is usually fruitless

9 Complications are not frequent and not particularly dangerous if treated by standard procedures

10 Three out of 4 patients were salvaged for further military duty

11 Except in a long time study of a large number of cases, inferences concerning the degree of tendency for pneumothorax to recur are not valid

12 The immediate or remote cause of this type of pneumothorax is still unsettled. The theories, spontaneous rupture of a weakened portion of the pleura, tearing of pleural adhesion, rupture of subpleural emphysematous blebs, interstitial emphysema leading to a subpleural collection and finally rupture<sup>3</sup> and wearing through of the pleura through the process of normal denudation,<sup>4</sup> have not been disproved. Conversely, none of these theories can be strongly advocated on the basis of these observations. The theories of a tearing of a pleural adhesion or rupture of an emphysematous bleb are not supported by these cases, since residual pleural adhesions and emphysematous blebs could not be demonstrated on the roentgenograms. However, judging from the work of others, the rupture of an emphysematous bleb still seems the most likely immediate cause. In addition, there was no demonstrable association with pulmonary tuberculosis.

13 So far as these data are concerned, there is no demonstrable relation between flying and spontaneous pneumothorax

3 Hamman, L. A Note on the Mechanism of Spontaneous Pneumothorax, *Ann Int Med* **13** 923-927 (Dec) 1939

4 Schomer, A., and Ehrlich, D. E. *M Bull Vet. Admin* **11** 206, 1935

# STREPTOMYCIN FOR CERTAIN SYSTEMIC INFECTIONS AND ITS EFFECT ON THE URINARY AND FECAL FLORA

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Streptomycin, an antibiotic substance derived from *Actinomyces griseus*, when injected parterally appears in the blood, urine and spinal fluid in amounts theoretically bacteriostatic or bactericidal for certain gram-negative bacilli known to be resistant to penicillin and to sulfonamide compounds<sup>1</sup>. When given orally, only traces appear in the blood and urine, since most of it is excreted in the feces, where it exerts a suppressive effect on various bacteria. It is relatively nontoxic. These facts, together with suggestive evidence of the therapeutic value of streptomycin in several cases of typhoid<sup>1a</sup> and in experimental infections in animals,<sup>2</sup> warrants further trial of the drug in several directions, namely, (a) for

more patients with typhoid, (b) for infections caused by gram-negative bacilli, especially brucellosis, bacillary dysentery, tularemia, plague, cholera and *Escherichia coli* and *Hemophilus influenzae* infections, (c) for infections of the urinary tract, and (d) to study its effect on the flora of the intestinal tract.

In this paper, report is made of the effect of streptomycin in 5 more patients with typhoid, 3 with brucellosis, 1 with tuberculous meningitis and 5 with infection of the urinary tract, and in 6 patients to study its effect on the flora in the feces. Including 5 patients in a previous report, streptomycin was given to 35 patients. Report of the use of streptomycin in 10 cases of cholera will appear elsewhere.

From the Jefferson Medical College and Hospital (Dr Reimann and Dr Price) and the Wyeth Institute of Applied Biochemistry (Dr Elias)

Streptomycin hydrochloride was generously supplied by Merck & Co, Inc, Rahway, N J. Mrs Jane Durso assisted with the technical details of the study.

1 (a) Reimann, H A, Elias, W F, and Price, A H. Streptomycin for Typhoid. A Pharmacologic Study, *J A M A* **128** 175-180 (May 19) 1945. (b) Elias, W F, and Durso, J. Blood, Urine, and Fecal Levels of Streptomycin in the Treatment of Human Infections of *E Typhosa*, *Science* **101** 589-591 (June 8) 1945. (c) Hinshaw, H C, and Feldman, W H. Streptomycin in Treatment of Clinical Tuberculosis. A Preliminary Report, *Proc Staff Meet, Mayo Clin* **20** 313-318 (Sept 5) 1945. (d) Anderson, D G, and Jewell, M. The Absorption, Excretion and Toxicity of Streptomycin in Man, *New England J Med* **233** 485-491 (Oct 25) 1945. (e) Zintel, H A, and others. Studies in Streptomycin in Man. I. Absorption, Distribution, Excretion and Toxicity, *Am J M Sc* **210** 421-430 (Oct) 1945. (f) Heilman, D H, and others. Streptomycin Absorption, Diffusion, Excretion and Toxicity, *ibid* **210** 576-584 (Nov) 1945. (g) Herrell, W E, and Nichols, D R. The Clinical Use of Streptomycin. A Study of Forty-Five Cases, *Proc Staff Meet, Mayo Clin* **20** 449-462 (Nov 28) 1945.

2 Heilman, F R. Streptomycin in the Treatment of Experimental Tularemia, *Proc Staff Meet, Mayo Clin* **19** 553-559 (Nov 29) 1944. Feldman, W H, and Hinshaw, H C. Effects of Streptomycin on Experimental Tuberculosis in Guinea Pigs, *ibid* **19** 593-599 (Dec 27) 1944. Heilman, F R. Streptomycin in the Treatment of Experimental Infections with Microorganisms of the Friedlander Group (*Klebsiella*), *ibid*

*Methods*—The preparation of solutions of streptomycin hydrochloride and the methods of its intravenous, intramuscular and oral administration were the same as described before<sup>1a</sup>. Assay of the amount of streptomycin in the blood, urine, feces and spinal fluid was made according to Stebbins' method<sup>3</sup>. The potency of the various lots of streptomycin used varied from 130 to 430 units per mg. Amounts of streptomycin recorded in these studies are expressed in terms of weight of pure streptomycin base according to the newly adopted plan whereby 1 microgram represents 1 unit and 1 Gm represents 1,000,000 units. Estimation of the number of bacteria in the urine and feces was made by standard methods.

## REPORT OF CASES

### TYPHOID

CASE 1—H B, a woman aged 33, was admitted to the Germantown Hospital, service of Dr Thomas Garrett, in a stuporous state with high fever and bacteremia with *Eberthella typhosa*. Streptomycin, 4 Gm daily, was given intravenously beginning on the tenth day of the disease. The temperature, which was 105 F (chart 1), declined during three days of therapy to 102 F, but the stupor deepened into coma and death occurred on the fourteenth day, after about 15 Gm had

**20** 33-39 (Feb 7) 1945. Smith, M I, and McCloskey W T. The Chemotherapeutic Action of Streptomycin and Promin in Experimental Tuberculosis, *Pub Health Rep* **60** 1129-1138 (Sept 28) 1945.

3 Stebbins, R B, and Robinson, H J. A Method for Determination of Streptomycin in Body Fluids. *Proc Soc Exper Biol & Med* **59** 255-257 (June) 1945.

been given Bacteremia persisted, although the amount of streptomycin in the blood varied from 11 to 22 micrograms per cubic centimeter (22 to 44 micrograms per cubic centimeter of serum), which amount was more than that needed (9 micrograms) to kill the same strain of *E typhosa* on agar Her spinal fluid contained 20 micrograms of streptomycin per cubic centimeter, and the usual 30 to 50 per cent of the amount injected was excreted in the urine

Although this severely sick patient was treated early in the disease with theoretically adequate amounts of streptomycin, the blood was not cleared of *E typhosa* and death occurred The typhoid bacillus from this patient

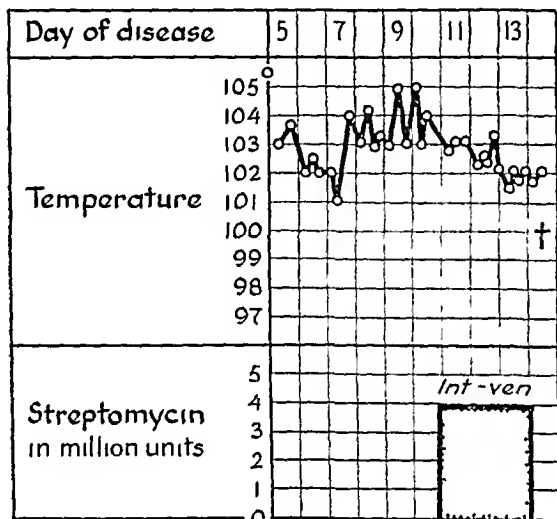


Chart 1 (case 1) —Typhoid The patient received 4 Gm. (4,000,000 units) of streptomycin intravenously for over three days but died despite the presence of 22 micrograms of streptomycin per cubic centimeter in the blood while only 9 micrograms killed the infecting bacillus in broth culture

was killed by 9 micrograms of streptomycin per cubic centimeter of agar, as compared with a stock strain, which was killed by 2 micrograms but not by 1 microgram, and with the strain obtained in the epidemic,<sup>1a</sup> which was inhibited by 6 micrograms

CASE 2—L B, aged 21, was admitted to the service of Dr Sumner Cross at the Abington Memorial Hospital on the fifth day of disease Although the temperature varied from 103 to 105 F, she never appeared to be toxic and was regarded as having a mild attack, although *E typhosa* was cultivated several times from the blood and from the feces Streptomycin in doses of 4 Gm daily was given intravenously, beginning on the twelfth day of disease Within thirty hours the temperature fell to normal and recovery occurred (chart 2) Amounts between 11 and 20 micrograms per cubic centimeter of blood were present during therapy An amount estimated as between 2 and 5 micrograms appeared in the spinal fluid Treatment was given in large doses for four days, after which the dose was reduced to 2 Gm and then to 1 Gm A total of about 19 Gm was given

Recovery seemed to have been brought about by streptomycin in this patient The infecting

bacillus, however, was more resistant than any other strains of *E typhosa* tested and withstood 16 micrograms of streptomycin per cubic centimeter but not 18 micrograms when cultured on agar This quantity was only slightly exceeded by the amounts measured in the blood Evidence in this case and in case 1 suggests that susceptibility of the infecting strain of *E typhosa* to streptomycin and the amounts of drug present in the blood bear no close correlation as regards the clinical outcome Therapeutic failure in case 1 occurred with a relatively sensitive strain and large amounts of drug in the blood, while recovery occurred in case 2 with the same dosage, but with lesser amounts in the blood and a more resistant strain Either the inhibition test is not sensitive enough for minor variations in resistance or other obscure factors in the host also play a role If, according to Goodpasture's view, typhoid bacilli reside and multiply intracellularly in plasma cells and macrophages, they may not be affected by streptomycin unless they escape into the blood or tissues

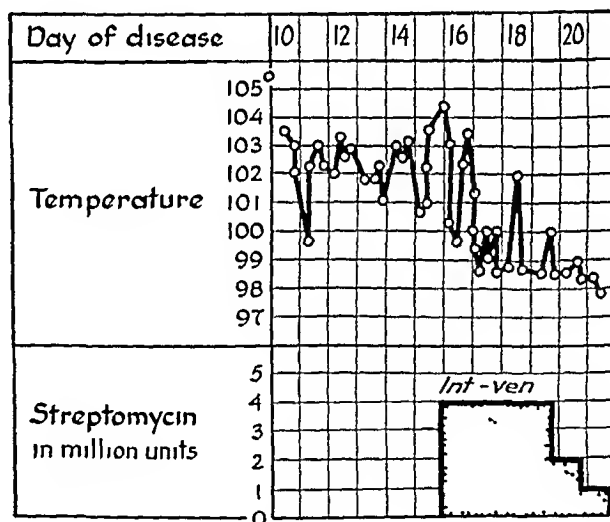


Chart 2 (case 2) —Typhoid The patient received 4 Gm (4,000,000 units) of streptomycin intravenously for four days and then smaller amounts Recovery occurred, but only 11 to 20 micrograms of streptomycin appeared in the blood, while as much as 18 micrograms per cubic centimeter was needed to kill the bacillus in broth culture

Three more patients, whose records need not be described in detail, were treated Two, whose temperatures declined slowly over a week and who recovered, received 20 Gm and 45 Gm respectively, and 1, who received 24 Gm, died

#### BRUCELLOSIS

If streptomycin is bacteriostatic or bactericidal for *E typhosa* in the body, it should, theoretically, be even more so for *Brucella suis*

since three strains from patients treated were killed on culture with as little as 0.5 microgram per cubic centimeter of agar, as compared with 6 to 18 micrograms needed to kill *E. typhosa* isolated from patients.

CASE 3—C M., a physician aged 41, had an attack of supposed grip lasting two weeks in February. He was then well until about March 1, when malaise, weakness, chilliness and fever (temperature 102 F) recurred. Later there were severe chills, drenching sweats, insomnia, headache, aching and constipation characteristic of a severe attack. The titer of a brucella agglutinin test was 1:640. Large doses of sulfadiazine and later of penicillin were given in spite of lack of evidence of their value for brucellosis. A course of injections of vaccine was likewise ineffective.

He was admitted to this hospital on the twenty-sixth day of the relapse, which began March 1. The important data are the fever chart (chart 3), leuko-

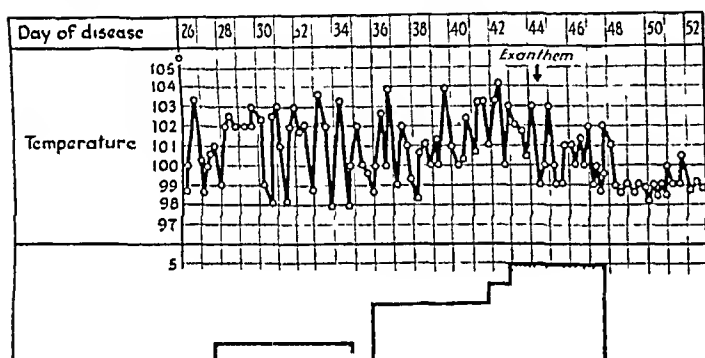


Chart 3 (case 3)—Brucellosis. There was no response to small doses of streptomycin intramuscularly or intravenously, but after the forty-second day, when 5 Gm (5,000,000 units) were given daily, the temperature began to decline. The Br. suis responsible was inhibited by as little as 0.5 micrograms per cubic centimeter of broth, the blood contained as high as 27 micrograms per cubic centimeter.

penia, agglutinin for brucella in titer of 1:2,000 (had received vaccine) and a blood culture positive for *Brucella suis*. The growth of this bacterium was inhibited by 0.5 microgram of streptomycin but not by 0.1 microgram per cubic centimeter of agar.

Because of previous experience with typhoid in which 12 micrograms per cubic centimeter of blood appeared after daily intramuscular injection of 1 Gm, this dosage was first used for seven days. Three cubic centimeters of a solution of streptomycin in distilled water (each cubic centimeter containing about 45,000 micrograms) was given every three hours. Aside from local pain no other untoward symptoms were noted. On this dosage only from 1 to 4 micrograms appeared in the blood, 40 per cent was excreted in the urine and none in the feces. Since no clinical improvement occurred, the dosage was increased to 3 Gm daily and given intravenously (chart 3). The amount in the blood rose to 9 and 13 micrograms per cubic centimeter of blood, but still there was no clinical improvement after six days. The dose was increased to 4 Gm and then to 5 Gm, with a rise in the amount in the blood to 27 micrograms per cubic centimeter, which is about sixty times the amount needed to kill the infecting bacilli in vitro. Doses of this size caused about 2,800 micrograms per cubic centimeter to appear in the urine and

11 micrograms per cubic centimeter in the spinal fluid but only traces in the feces. There was no evidence of toxicity other than a diffuse erythematous eruption lasting twelve hours on the forty-fourth day.

After dosage at 5 Gm was begun, the fever gradually declined for five days and ended abruptly on the forty-eighth day, with coincident clinical improvement. A total of about 54 Gm of streptomycin was given. The patient returned to his home on April 23, after six days without a rise of temperature over 99 F. During the second week the temperature occasionally rose to 101 F and once to 102.3 F. In the third week, there were occasional chills with spikes of temperature to 104 F, but the patient felt well enough to get out of bed. Thereafter recovery took place.

In this instance the sensitivity of the infecting *Brucella* to streptomycin on agar was not a reliable guide to the amount needed in the blood to control the infection. Recovery in this patient was probably spontaneous and not related to therapy, yet the fever declined during treatment after large doses were used. The subsequent recrudescence shows that the infection persisted and suggests the need for continuing treatment for some time after defervescence.

CASE 4—G V B., aged 31, a veterinary assistant, noted slight fever in mid-April, which persisted and increased until he was admitted to Abington Memorial Hospital, May 5, as a patient of Dr. E. S. Vollmer.

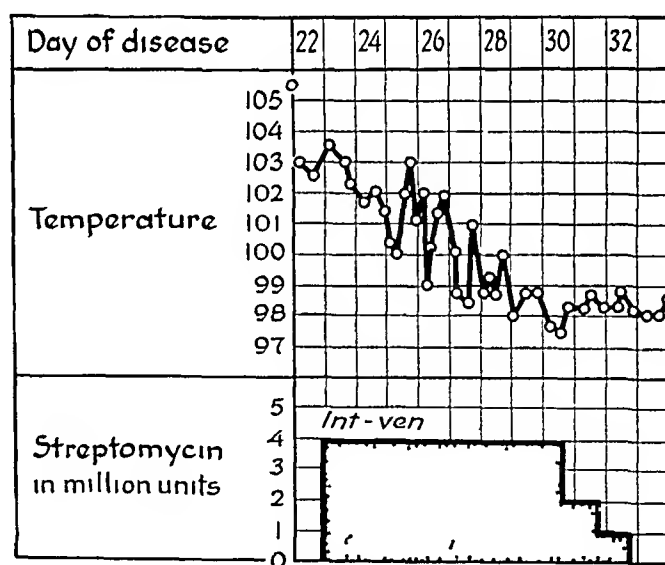


Chart 4 (case 4)—Brucellosis. There was prompt defervescence and recovery during treatment with 4 Gm (4,000,000 units) of streptomycin intravenously. Br. suis was killed by 0.5 microgram per cubic centimeter of broth, the blood contained 12 to 19 micrograms per cubic centimeter.

Drenching sweats occurred and fever increased to 104 F. Physical examination revealed nothing essentially abnormal except that the patient appeared to be severely sick. The leukocytes numbered 5,000, and 60 per cent were lymphocytes. The serum agglutinated *Brucella* in a titer of 1:360, and Br. suis grew in a culture of the blood. The patient was transferred to this hospital on May 10, about the twenty-second day of disease.

Because of the experience in case 3, therapy was started with large dosage. Streptomycin was given intravenously in doses of 4 Gm daily. Shortly thereafter, the temperature began to decline steadily until it reached normal on May 17, after six days of treatment with 24 Gm. The dose was then reduced to 2 Gm, then to 1 Gm (chart 4). The amount of streptomycin in the blood varied from 12 to 19 micrograms per cubic centimeter, and in the serum from 25 to 35 micrograms. The infecting *Brucella*, as in case 3, was inhibited by 0.5 microgram of streptomycin per cubic centimeter of agar.

The appearance of the temperature curve (chart 4) and the clinical improvement strongly suggest that streptomycin played a role in the recovery. No relapse has occurred to date.

CASE 5—A A, aged 6, was noted by her parents to have fever, gradually rising to 104 F, in February 1945. She recovered after several weeks and was apparently well until April 28, when fever recurred, and on May 5 she entered the Jewish Hospital as a patient of Dr. Schless. Her temperature rose to 104 F. It gradually fell to normal after a week, remained normal for four days and rose again to 105 F. During this time no other physical abnormalities except pallor, sweating and hepatomegaly were noted. The leukocytes numbered 6,000, and 65 per cent of them were lymphocytes. Agglutination for *Brucella* occurred in a titer of 1:160. A cutaneous test with *brucella* vaccine elicited a strongly positive reaction. A diagnosis of brucellosis was made, and the patient was transferred to this hospital for treatment.

At this time, about the nineteenth day of the current bout, the temperature was 105 F, the leukocytes numbered 5,000, 60 per cent of which were lymphocytes, agglutinins for *brucella* were present in titer of 1:500 and a blood culture was positive for *Brucella abortus*. The child weighed 25 Kg (62 pounds).

Streptomycin, 3 Gm daily, a large amount in proportion to her weight, was given by the intravenous drip method and continued for about eight days (24 Gm). Only 12 micrograms per cubic centimeter was present in the blood. No beneficial effect resulted. The *Br. abortus* involved was inhibited by 0.5 but not by 0.1 microgram of streptomycin in agar.

#### TUBERCULOUS MENINGITIS

During the course of these studies, the amount of streptomycin was measured in the spinal fluid of several patients, as noted incidentally in certain case reports and listed in table 1. Assuming the meninges to be unaffected in each instance, it is obvious that streptomycin injected parenterally enters the spinal fluid in variable, but in theoretically bactericidal, amounts, as shown in table 1. In case 1 twice the amount appeared with 4 Gm doses as with 5 Gm in case 3.

It is questionable whether it is more important to attain a high concentration of the drug in the spinal fluid by intrathecal injection rather than in the meningeal and other tissues by the parenteral route for the treatment of meningitis. Experience with penicillin in the treatment of

bacterial meningitis reported elsewhere<sup>4</sup> indicated that parenteral therapy suffices and that intrathecal injection is unnecessary.

CASE 6—J M, aged 15, a patient of Dr. W. Daiber, complained of headache about April 7 which became much worse, with fever and signs of meningitis. The spinal fluid on two occasions was under pressure of 600 mm of water, contained 200 leukocytes, mostly lymphocytes, 44 and 30 mg of sugar, and 640 and 600

TABLE 1—Amounts of Streptomycin in the Spinal Fluid after Various Parenteral Doses Compared with Amounts in the Blood

Case	Daily Dose, Gm	Micrograms per Cc of Spinal Fluid	Micrograms per Cc of Blood
O G *	1, intramuscularly	5 (estimated)	5 (estimated)
9 J S	1, intravenously	4 (estimated)	
1 H B	4, intravenously	20	12
2 L B	4, intravenously	5 (estimated)	20
3 C M	5, intravenously	11	30
	5, intravenously	6 (estimated)	14
6 J M	4, intravenously	16	19
(tuberculous meningitis)		20	
		18	
		18	
		18	

\* Reimann, Llus and Price,<sup>1</sup> case 1.

mg of chloride. A pellicle formed, and in one specimen acid-fast rods were reported. Cultures of the spinal fluid remained sterile. In later samples the amount of sugar present was too small to measure.

On the twenty-fifth day of disease streptomycin was given by continuous intravenous drip, 4 Gm daily, for seven days. No significant changes occurred in the spinal fluid, somnolence deepened into coma and death occurred on the thirty-second day. The diagnosis was confirmed at necropsy. During therapy the amount of streptomycin in the spinal fluid measured on five occasions varied from 16 to 20 micrograms per cubic centimeter.

#### EFFECT OF STREPTOMYCIN ON THE FLORA OF THE URINE

The fact that from 40 to 60 per cent of streptomycin injected parenterally is excreted in the urine where it appears in bactericidal amounts, suggests its therapeutic trial in cases of infection of the urinary tract caused by gram-negative bacilli. Plans were made accordingly to study the effect of streptomycin on the bacteria in infected urine. Intramuscular or intravenous injection of between 1 Gm and 5 Gm causes 150 to 2,800 micrograms of streptomycin per cubic centimeter to appear in urine, depending on the volume of urine (table 2). In this respect, intramuscular therapy and a restricted intake of fluid, to obtain a relatively large amount of drug in a small amount of urine,

4 Price, A. H., and Hodges, J. H. Treatment of Meningitis with Penicillin Injected Intravenously and Intramuscularly, New York State J. Med. 44: 2012-2014 (Sept. 15) 1944.

is usually preferable to intravenous therapy, which requires the daily injection of 3,000 cc of fluid. However, in 1 patient the intravenous injection of 5 Gm resulted in 2,800 micrograms of streptomycin per cubic centimeter of urine, the highest amount measured. Considerable daily variation occurs even with constant dosage, as indicated by sample readings shown in table 2.

TABLE 2—Variations in Amount of Streptomycin per Cubic Centimeter of Urine in Relation to Dosage, Route of Injection and Amount of Urine Excreted

Case	Daily Dose, Gm	Micrograms per Cc of Urine	Daily Urinary Output, Cc
3 C M	1, intramuscularly	150	2,650
		280	2,800
	3, intravenously	540	4,300
		2,500	2,780
	5, intravenously	2,800	3,440
10 J W	1, intramuscularly	300	1,200
	2, intramuscularly	1,700	1,300
9 J S	1, intramuscularly	115	1,100
	1, intravenously	150	3,600
7 B B	2, intravenously	310	3,800
		640	4,000
4 G B	4, intravenously	700	3,100
		1,630	810
		700	3,700

Amounts accumulate rapidly in the urine within a few hours after beginning treatment and disappear about forty-eight hours after stopping it.

#### BACILLUS PYOCYANEUS INFECTION

CASE 7—Mrs B B, aged 32, had hydronephrosis and pyuria, with gram-negative rods and gram-negative cocci in the urine. On culture only colonies of *Bacillus pyocyaneus* grew. Shortly after operation for dilation of the urethra and urethral orifices, the temperature rose to 106 F and the leukocytes to 12,000 per cubic millimeter of blood. Streptomycin was given by the intravenous drip method in doses of 2 Gm daily for four days. During this time the temperature rapidly declined to normal. Before treatment the number of *B. pyocyaneus* organisms estimated in the urine was 2,000,000; forty-eight hours after the beginning of treatment, the number was reduced to 2,000 and on the fourth day to 1,500. The amount of streptomycin in the urine varied from 300 to 640 micrograms per cubic centimeter, representing the usual 40 to 60 per cent recovery of parenterally injected streptomycin. Growth of the *B. pyocyaneus* involved was inhibited on agar containing 100 micrograms per cubic centimeter but not 75 micrograms.

CASE 8—C G, a debilitated man aged 66, studied in collaboration with Dr John Reimann at Abington Memorial Hospital, had a severe infection of the urinary tract with *B. pyocyaneus* and *Bacillus proteus morganii*. He was given 4 Gm daily intravenously for five days, but edema developed and the intramuscular route was chosen. His general condition became worse, and treatment was stopped.

Culture of the urine during treatment showed a disappearance of *Proteus morganii*, which was inhibited

by 8 micrograms per cubic centimeter of agar, but *B. pyocyaneus* which was on test was resistant to more than 200 micrograms per cubic centimeter. Evidently different strains of *B. pyocyaneus* also vary in their resistance to streptomycin.

#### EBERTHELLA INFECTIONS

CASE 9—J S, a man aged 48, suffered from chronic infection of the urinary tract after a pelvic injury four years previously. He complained of frequent burning, and his urine was often cloudy. A stained smear showed a mixture of bacteria, mostly gram-negative rods, and variable other bacilli, which on culture were *E. coli* (predominant), *Klebsiella pneumoniae* and a hemolytic gram-positive rod. The numerical distribution of bacteria before and after treatment with streptomycin is shown in table 3. The colon bacillus isolated was inhibited by 3 micrograms but not by 2 in the test tube.

The patient's urinary output was diminished by limiting the fluid intake to 1,000 cc per day in order to concentrate the excreted streptomycin. The drug was given intramuscularly in doses of about 0.125 Gm every three hours, or 1 Gm daily. Pain at the site of injection and slight headache occurred shortly after the first dose. Each of the next five injections was followed by severe headache lasting about thirty minutes. After two days of intramuscular therapy because of headache, the same dosage was given by the intravenous route for four days. No further headache occurred, probably because of more gradual administration of the drug. The effect on the bacterial count is shown in table 3. Within twenty-four hours urine was free from all bacteria, including the gram-positive bacilli, except anaerobic ones.

Tests were made to determine the lasting effect of therapy on the urinary flora. Two days after treatment was stopped, a trace of streptomycin was still present in the urine to account for the persistent absence of certain unidentified aerobic bacteria, yet when the urine was diluted to reduce the amount of drug present, the hemolytic bacilli grew, indicating that streptomycin had a suppressive but not a bactericidal effect. No colon bacilli grew at any dilution. Seven days after treatment was stopped neither colon bacilli nor the hemolytic bacilli grew on the culture plates.

The spinal fluid contained 4 micrograms of streptomycin per cubic centimeter with doses of 1 Gm daily intravenously.

CASE 10—J W, a man aged 65, had urinary retention complicated by prostatic hypertrophy and obstruction. A retention catheter was inserted for drainage. The urine was purulent and contained a variety of bacteria as indicated in table 4. The colon bacillus present was inhibited by 6 micrograms of streptomycin but not by 5 micrograms.

The fluid intake was restricted to 1,200 cc a day, and streptomycin was given intramuscularly in doses of 2 Gm for two days. Injections were followed immediately by pain locally and moderate headache lasting thirty minutes accompanied with a temporary fall of blood pressure from 128 systolic and 78 diastolic to 110 systolic and 40 diastolic and once to 90 systolic and 40 diastolic. The dosage was reduced to 1 Gm for four days with only occasional mild headache after injection. The effect of therapy on the bacteria in the urine is illustrated in table 4. As in case 9, within twenty-four hours the urine was cleared of all bacteria except anaerobic ones.

Higher dilutions of urine made from the sample of the third day of treatment gave growth of a few colonies

of various unidentified aerobic bacteria, indicating that the streptomycin present in undiluted urine inhibited their growth but when it was further diluted growth occurred. *E. coli* failed to grow in any dilution.

Samples tested two days after treatment was stopped still contained traces of streptomycin, and the total aerobic bacterial count increased to 32,000,000, but colon bacilli were absent. Seven days later colon bacilli and hemolytic cocci were both absent.

In 1 patient, 4 Gm of streptomycin given intravenously failed to eliminate *E. pyogenes* from the urine, although 1,500 units were present in it.

#### EFFECT OF STREPTOMYCIN ON FLORA OF THE FECES

Streptomycin given orally is almost all excreted in the feces. In studies in a case of typh-

Streptomycin was given orally every three hours to each patient, the amount depending on the total daily dose decided on.

CASE 11—Mrs. G. S. was given 2 Gm of streptomycin by mouth daily in doses of 0.25 Gm every three hours for three days before operation for carcinoma of the colon with subacute obstruction. Bacterial counts made before treatment showed 1,300,000 organisms on nutrient agar, 16,000,000 in anaerobic culture medium and 10,000 colon bacilli on MacConkey's medium. Feces passed during the first twenty-four hours of therapy contained 650 micrograms of streptomycin per gram, the number of bacteria on nutrient agar and on culture medium for anaerobes was unchanged, but colon bacilli were absent. Stools passed during the second twenty-four hours contained 850 micrograms per gram with the bacterial growth about the same, no colon bacilli grew.

CASE 12—Mrs. R. H. was given the same daily dosage of streptomycin as in case 11 for two days before opera-

TABLE 3 (case 9, J. S.)—Effect of Parenteral Therapy on Urinary Flora

Day	Dose, Gm	Urine Volume, Cc	Micrograms per Cc	Total Aerobic Count	Coliform Bacilli	Hemolytic Bacilli	Anaerobic Bacteria
Before treatment				5,000,000	600,000	500,000	700,000
1	1 intramuscularly	1,100	110	0	0	0	Present
3	1 intravenously	980	770	0	0	0	Present
4	1 intravenously	2,170	120	0	0	0	Present
6	1 intravenously	3,600	150	3,200	0	0	Present
Two days after treatment				2,000,000	0	0	Very few present
Nine days after treatment				2,000,000	0	0	

TABLE 4 (case 10, J. W.)—Effect of Parenteral Therapy on Flora of the Urine

Day	Dose, Gm	Urine Volume, Cc	Micrograms per Cc	Total Aerobic Count	<i>E. coli</i>	Hemolytic Cocci	Anaerobic Bacteria
Before treatment				7,000,000	5,000,000	2,000,000	1,000,000
1	2 intramuscularly	1,450	150	0	0	0	Present
2	2 intramuscularly	1,320	1,700	0	0	0	0
3	1 intramuscularly	2,600	300	0	0	0	Present
6	1 intramuscularly	1,200	300	18,000,000	0	0	Present
8	2 days after treatment		13	32,000,000	0	8,000	Present
15	9 days after treatment		None	8,000	0	0	Present

oid (Reimann, Elias and Price<sup>1</sup> case 5) oral administration of 4 Gm daily caused from 10,000 to 20,000 micrograms of streptomycin to appear per gram of the feces and eliminated both *E. typhosa* and *E. coli* from the feces during treatment, giving an almost odorless stool. Both varieties of bacilli reappeared several days after oral therapy was stopped, when only 40 micrograms of streptomycin per gram of feces remained. It was suggested that for intestinal infections susceptible to the effects of streptomycin, the drug should be given parenterally to control the systemic infection and orally to sterilize the feces and prevent reinfection.

The results also suggested that streptomycin may be of value to reduce the number of susceptible bacteria in the intestine prior to surgical operation. With this in mind the following patients were treated and studied.

For carcinoma of the colon with subacute obstruction. Before therapy too many bacteria to count grew on all three mediums. After twenty-four hours of treatment the stools contained 3,200 micrograms per gram with a reduction to 1,000,000 colonies on nutrient agar and slight reduction, to 100,000,000 on anaerobic mediums, but no colon bacilli grew. The next day, with 600 micrograms per gram, the count was 400,000 on nutrient medium, there was no reduction in anaerobic culture and again no colon bacilli.

In these 2 patients, 600 micrograms of streptomycin per gram of feces was enough to eliminate colon bacilli. At operation the surgeons found the bowel not distended and well prepared for operation.

CASE 13—Mrs. K. S., aged 65, a diabetic patient with carcinoma of the colon, was given 1 Gm orally for seven days. The amount of streptomycin in the feces varied from 1,000 to 5,800 micrograms per gram but was without effect on the numbers of any bacteria, including *E. coli*, as compared with a sample plated

before treatment Dosage was increased to 2, 3, 4, 5 and finally 6 Gm at intervals of several days At 5 Gm the amount of streptomycin rose to 16,000 micrograms per gram but again without significant influence on the numbers of bacteria, as shown in table 5

Only after the dose of 6 Gm were the counts significantly reduced The failure to eliminate these colon bacilli was perhaps accounted for by their resistance to streptomycin, they grew on agar containing 200 micrograms of streptomycin per cubic centimeter, while growth of colon bacilli in cases 11 and 12 was inhibited by 6 micrograms

CASE 14—Mrs B E, aged 65, with carcinoma of the colon, had a count of 4,000,000 aerobic bacteria and 3,000,000 E coli She received 5 Gm of streptomycin daily for two days After twenty-four hours of treatment no aerobic bacteria and no colon bacilli grew Anaerobic bacteria were unaffected On the first and second days 400 micrograms and 760 micrograms of streptomycin respectively were present per gram of feces

CASE 15—E B, with carcinoma of the colon, had 10,000,000 anaerobic bacteria and 6,000,000 E coli per gram of feces He was given 5 Gm of streptomycin orally for five days After forty-eight hours of treatment the number of aerobic organisms was reduced

temic infections caused by certain gram-negative streptomycin-sensitive bacilli which are not influenced by penicillin or sulfonamide compounds, since the amounts attained in the body by parenteral or oral administration often exceed the amounts needed to kill these bacilli on agar Yet for infections caused by relatively less sensitive bacilli, like E typhosa, the clinical results thus far reported are not as satisfactory as desired No benefit occurred in some instances in which the amount of streptomycin in the blood greatly exceeded the theoretic bactericidal level early in the disease (case 1), and in 1 instance (case 2) an apparent good result was obtained in infection with a strain of E typhosa which resisted 16 micrograms of streptomycin in vitro The matter is further complicated by evidence of considerable variation in resistance to streptomycin (1 to 18 micrograms per cubic centimeter) of different strains of E typhosa, by

TABLE 5 (case 13, K S)—Effect of Oral Therapy on Resistant Bacteria in the Feces

Days	Oral Dosage, Gm	Weight Feces, Gm	Micrograms per Gm Feces	Nutrient Medium	MacConkey's Medium	Anaerobic Bacteria
Pretreatment				41,000,000	27,000,000	Uncountable
2	1	182	2,700	56,000,000	70,000	
7	1	41	5,800	270,000,000	115,000,000	80,000,000
9	2	258	9,100	170,000,000	125,000,000	16,000,000
11	4	289	3,700	315,000,000	78,000,000	200,000,000
15	5	57	16,400	400,000,000	100,000,000	Many
17	5	238	5,200	300,000,000	120,000,000	Many
18	6	36	1,900	1,000,000	250,000	Present

to 50,000 and colon bacilli to 0, while 3,300 micrograms of streptomycin was present per gram of feces

CASE 16—D R, with carcinoma of the colon, before treatment had 1,000,000,000 each of aerobic bacteria and E coli per gram in his feces After one day of 5 Gm of streptomycin, only 10,000 aerobic bacteria and no colon bacilli remained in the feces, which contained 6,500 micrograms of streptomycin per gram

The surgical aspects of the treatment and its effect in these patients will be the subject of a separate report

Streptomycin was given orally in doses of 5 Gm daily for seven days to a patient with severe ulcerative colitis During therapy the number of stools lessened but the fever persisted unchanged

#### TOXICITY

In these studies the only evidence of toxicity of streptomycin was transient but severe headache in 2 patients treated intramuscularly (cases 9 and 10), headache and a fall in blood pressure in 1 and erythema in 1 treated intravenously (case 3)

#### COMMENT

There is reason to believe that streptomycin holds promise as a therapeutic agent for sys-

TABLE 6—Resistance to Streptomycin of Bacteria Isolated During this Study

Case	Strain	Micrograms of Streptomycin Not Inhibitive	Micrograms of Streptomycin Which Inhibit
	Stock, E typhosa		1
Epidemic*	E typhosa	4	6
1 H B	E typhosa	7	9
2 L B	E typhosa	16	18
3 C M	Br suis	0.1	0.5
4 G B	Br suis	0.1	0.5
5 A A	Br suis	0.1	0.5
7 B B	B pyocyaneus	75	100
8 C G	B pyocyaneus	>200	
	P morgani	7	8
9 J S	E coli	2	3
10 J W	E coli	5	6
13 K S	E coli	>200	

\* Reimann, Elias and Price<sup>1</sup>

irregularities in the amounts of streptomycin attained in the body with similar dosage in the same patient and in different patients, by the possibility that intracellular bacteria may not be affected by the drug, by the possibility of the development of drug resistance by the bacteria during treatment, by the possibility that the hydrogen ion concentration of autolysing tissues and pus may be low enough to inactivate basic

streptomycin,<sup>5</sup> and by the probable variation in the lots of streptomycin available at present. In certain instances as much streptomycin was measured in the blood after the injection of 1 Gm intramuscularly as with 5 Gm given intravenously, and increases of dosage were not always followed by proportionate increments in the blood. Amounts in the blood did not exceed 27 micrograms per cubic centimeter in any of the patients studied. It is evident that many more patients with typhoid treated with streptomycin must be studied before its value can finally be assessed.

Even less can be said at present for the treatment of brucellosis from studies in only 3 cases. Despite the fact that B1 suis obtained from patient 3 was far more sensitive to streptomycin in vitro than *E. typhosa*, no beneficial effect was apparent until sixty times the theoretic amount needed was attained in the blood. Even then, the forty-eighth day of disease, a spontaneous remission may have clouded the issue. In case 4 recovery may also have been spontaneous, but it appears very likely that the disease was terminated by streptomycin, although amounts of only 19 micrograms per gram of blood were attained. In case 5 no beneficial effect occurred, although the patient for her size received more streptomycin per kilogram than any other one. Similar uncertain results were reported by Herrell and Nichols.<sup>15</sup>

No benefit occurred in the patient with tuberculous meningitis in whom as much as 20 micrograms per cubic centimeter appeared in the spinal fluid. Nevertheless, amounts of streptomycin theoretically inhibitive for certain bacilli do appear in spinal fluid during parenteral therapy.

Streptomycin was an effective agent for reducing the numbers of or eliminating certain gram-negative bacilli from the urine in several patients when it was injected parenterally, but, again, the problems of the irregular amounts of drug which appear in urine and of variability of resistance of strains even of the same genus of bacteria arise. Of two strains of *B. pyocyaneus*, the one which was not eliminated by therapy was more than twice as resistant to the drug as the other. In 2 other patients *E. coli*, and in a third *B. proteus morganii*, were promptly eliminated with ease. The resistance to streptomycin on agar of various bacteria from patients in this study is presented in table 6.

Streptomycin given orally promptly suppresses or eliminates drug-sensitive strains of *E. coli* and *E. typhosa* and certain other bacteria from the feces so long as an adequate amount is maintained therein. Cessation of treatment is followed by rapid return of the flora, as may be expected, but even a temporary suppression is of value at times, particularly during intestinal operations. Here again in the few patients studied there was evidence of great variability in the resistance of different strains of *E. coli* to streptomycin, in most cases they were suppressed or temporarily eliminated, but in 1 diabetic patient a strain resistant to 200 micrograms per cubic centimeter of agar (the highest concentration tested) persisted in the stool despite the presence of 16,000 micrograms per gram of feces. Besides variation in bacterial resistance and in hydrogen ion concentration the matter of uniform admixture of streptomycin with feces must be considered. For better distribution, small doses fed often are probably better than large doses at longer intervals. No information is available about the amount of streptomycin which adheres to the wall of the bowel and of its effects on bacteria in the crypts or on the mucosal surface.

The relative value of streptomycin and other urinary and intestinal tract antiseptics, such as mandelic acid, sulfonamide compounds and penicillin, will have to be determined by further work. It can be said, however, that streptomycin is probably much less apt to cause toxic effects than the sulfonamide compounds. It may approach even closer to being the ideal intestinal antiseptic than ones now used since it is poorly absorbed from the digestive tract, it is nontoxic and eliminates certain pathogenic gram-negative bacteria from the feces.

#### SUMMARY

Streptomycin seemed to be of value in the treatment of 6 of 10 patients with typhoid reported on in this and in a previous study<sup>1a</sup>, no improvement from therapy occurred in 2, and 2 died. Different strains of typhoid bacilli vary in their resistance to streptomycin. There is evidence also that certain factors in the body inhibit the action of the drug or protect the bacteria from its effects.

The results of treatment of 3 patients with brucellosis are inconclusive. Recovery seemed related to therapy in 1 and doubtfully related in a second, and no benefit occurred in the third. No effect was noted against tuberculous meningitis, but streptomycin appears in the spinal fluid in theoretically bacteriostatic amounts for

<sup>5</sup> Florey, H. W. The Use of Micro-Organisms for Therapeutic Purposes, *Brit. M. J.* 2: 635-642 (Nov. 10) 1945.

certain bacteria when injected parenterally, whether the meninges are normal or diseased

Streptomycin in adequate dosage given parenterally promptly suppressed or eliminated *B. pyocyaneus*, *B. proteus morganii* and *E. coli* from the urine of several patients but only when these bacteria were of strains susceptible to the amounts of streptomycin present in the urine

Streptomycin given orally promptly suppressed or eliminated *E. coli* and certain other bacteria in the feces during therapy but failed to do so when the bacteria were resistant to the amounts of drug present

With similar dosages, irregularities in the amounts of streptomycin in the blood, urine, spinal fluid and feces occur in the same patient and in different patients. Within limits, the sensitivity of certain bacteria to streptomycin in culture mediums was not a reliable guide to the amount needed to suppress them in the body, but with highly resistant forms, and occasionally with susceptible forms, therapy was ineffective. It is probable that certain factors in the body interfere with the bacteriostatic action of streptomycin.

# HEMOLYTIC STREPTOCOCCUS SORE THROAT

## DETAILED STUDY OF THE SIMULTANEOUS INFECTION OF A LARGE NUMBER OF MEN BY A SINGLE TYPE

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Clinicians interested in infectious disease are aware that the exposure of a group of human beings or animals to an infectious agent will be followed by the development of clinical syndromes of varying degrees of severity. It is rarely possible to describe these phenomena in detail in human beings, since artificial inoculation is infrequently performed and since natural infection is usually unsuitable because the size of the infecting dose and the strain of micro-organism may be expected to vary from case to case. These difficulties are particularly evident in the study of group A hemolytic streptococcus infections, since many serologic types are known to occur among these organisms.

One of us has previously described<sup>1</sup> certain clinical and immunologic aspects of the disease resulting from the simultaneous infection of a large group of men by a single type of hemolytic streptococcus. Clinical observations in that epidemic were incomplete. Recently another opportunity for the study of a similar outbreak presented itself. This was a food-borne epidemic of type 1 hemolytic streptococcus sore throat which occurred among the patients of a large station hospital. More than 250 cases of clinical infection were discovered. A man working in the kitchen who was a carrier of type 1 streptococci in the nose and throat was believed to be the primary source of the infectious agent. On this occasion a smaller group of men was selected and studied in detail.

The laboratories of the Department of Medicine, Stanford University School of Medicine, were made available to the commission for certain studies.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

- 1 (a) Bloomfield, A L, and Rantz, L A. An Outbreak of Streptococcal Sore Throat in an Army Camp, *J A M A* **121** 315 (Jan 30) 1943. (b) Rantz, L A. Group A Hemolytic Streptococcus Antibodies. III. A Study of the Simultaneous Infection of a Large Number of Men by a Single Type, *Arch Int Med* **73** 238 (March) 1944.

## MATERIALS AND METHODS

Fifty-eight hospital patients, all suffering from functional gastrointestinal disease, were selected for study. They were particularly suitable for this purpose, since a complete laboratory work-up, including leukocyte count and erythrocyte sedimentation rate, had been previously performed in each case. An analysis of their diets indicated that all had been equally exposed to infection. The first clinical evidence of the outbreak was noted on April 16, 1944. Each of the study group was carefully examined and materials from the throat obtained for culture on April 17 and 18. Those who were found to harbor hemolytic streptococci in the nasopharynx were accepted for more detailed study, including close clinical observation and serial cultures of materials from the throat, Dick tests, leukocyte counts, measurements of erythrocyte sedimentation rate (Westergren) and antifibrinolysin<sup>2</sup>, and antistreptolysin titrations<sup>3</sup> over a period of twenty-four to thirty days. The isolated hemolytic streptococci were grouped and typed by the precipitin technics of Lancefield<sup>4</sup>.

## RESULTS

Group A hemolytic streptococci were discovered on the initial examination in the throats of 40 of the 58 men in the study group. In 5, the organisms were not strains of the epidemic type, and these patients were not further considered. Thirty-five persons had presumably become carriers of type 1 organisms as a result of exposure to infected food.

It was not possible to determine all the factors that prevented the epidemic type from gaining lodgment in the throats of 40 per cent of these men, but the most important factor was the absence of tonsils. These organs had been removed from 12, or 52 per cent, of the uninfected but from only 2, or 5.7 per cent, of the infected men.

- 2 Boisvert, P J. The Streptococcal Antifibrinolysin Test in Clinical Use, *J Clin Investigation* **19** 65, 1940.

- 3 Rantz, L A, and Randall, E. A Modification of the Antistreptolysin Determination, *Proc Soc Exper Biol & Med* **59** 22 (1945).

- 4 Lancefield, R C. A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, *J Exper Med* **57** 571, 1933. Swift, H F, Wilson, A T, and Lancefield, R C. Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, *ibid* **78** 127, 1943.

TABLE 1—Summary of Clinical, Clinicopathologic and Immunologic Observations on Thirty-Five Men Who Became Carriers of Type 1 Hemolytic Streptococci

Maximum Tempera- ture, Nearest Fahr Degree	Number of Cases	Subjective Sore Throat				Tonsillar Exudate				Tender Cervical Adenitis				Average Duration Fever, Days	Average Duration Objective Signs, Days	Total Leukocyte Count				Erythrocyte Sedimentation Rate (Westergren)				Positive Dick Test, Number	Antistreptolysin Titer					
		No		%		No		%		No		%				Range Highest Counts, × 1,000	Average Maximum Count, × 1,000	Significant Increase	Range Average		Most Rapid Rates, Mm / Hr	Significant Increase	No		%	Average Initial, Units/ Cc	Average Maximum, Units/ Cc	Average Fold,	No	%
		No		%		No		%		No		%																		
		No		%		No		%		No		%																		
		No	%	No	%	No	%	No	%	No	%	No	%			No	%	No	%	Cc	Units/ Cc	Units/ Cc	Increase		Increase	Increase	Increase			
103+	8	8	100.0	8	100.0	7	87.5	2.6	4.4	14.20	17.3	8	100.0	7.45	39	7	87.5	0	97	250	2.5	7	100.0							
102	6	6	100.0	4	66.6	5	83.4	2.5	3.3	7.20	14.5	5	83.4	5.26	12	4	66.6	1	160	284	1.8	5	83.4							
101	5	5	100.0	5	100.0	4	80.0	2.4	3.0	9.21	16.8	3	60.0	4.35	15	2	40.0	2	118	145	1.2	1*	33.3							
100	5	3	60.0	4	80.0	3	60.0	1.6	4.0	11.15	13.0	5	100.0	3.18	8	0	0.0	1	120	180	1.5	4	80.0							
99	6	4	66.6	4	66.6	3	50.0	1.2	2.3	8.15	10.8	2	33.3	1.68	18	3	50.0	3	58	110	1.9	4	80.0							
98.6	5	2	40.0	1	20.0	1	20.0	0.0	1.2	9.18	12.4	1	20.0	1.22	7	1	20.0	0	105	192	1.8	2	40.0							

\* Two were followed for less than one week

Streptococci of type 1 were present in the throat in large numbers for at least one week in all but 2 patients. A persistent carrier state may, therefore, be said to have been established.

**Clinical Observations**—Disease of widely varying degrees of severity occurred among the men infected by the epidemic streptococcus. The pertinent data are summarized in table 1. The cases have been divided into groups on the basis of the nearest whole Fahrenheit degree of the maximum recorded temperature. Subjective sore throat was present in every patient whose temperature was greater than 100 F, in 60 per cent of those with lesser degrees of fever and in 2 of the 5 whose temperatures remained normal throughout.

Tonsillar and pharyngeal exudate and tender anterior cervical adenitis have been the two most valuable signs for the clinical recognition of hemolytic streptococcus sore throat. The frequency of their occurrence in this group was roughly correlated with the height of fever, both being present more frequently and in a more definite form in patients whose temperature reached 101 F. One or the other of these signs was definitely present in all but 2 of the patients in whom a rise in temperature occurred. The latter men were definitely infected, since an antistreptolysin response was demonstrated during convalescence. Either exudate or adenitis was absent in several of the most severely ill patients, in all of whom the tonsils were intact. In others these signs were discovered only by the most careful examination.

The disease in the definitely febrile patients ran a short course, the temperature being elevated for an average of from two and five-tenths days in the most severely ill to one and two-tenths days in the least sick. The objective signs in the throat and the adenitis persisted for one or two days after the fever had disappeared.

The total leukocyte count on the second day of the disease was increased in nearly all febrile patients and in a few of the afebrile ones. The number was correlated with the maximum temperature, but a few men with a definite febrile illness failed to respond to the infection with an increase of these cells in the blood. The rate of erythrocyte sedimentation on the second day of illness was elevated for many patients and was greatest for those patients with temperatures above 103 F. A significant increase of 10 mm per hour or more was observed in about half of all patients and in 4 of the 11 in whom little or no fever was detected.

**Antibody Response**—An increase in the amount of antistreptolysin during convalescence was observed in only 1 case. This is in accord

with data obtained in other cases of type 1 infections and may be correlated with the weak fibrinolysin produced in vitro by these organisms

Seven of the 35 patients who became carriers of type 1 organisms and in whom definite evidence of infection was obtained had positive Dick reactions. In none did a rash develop, and cutaneous sensitivity was not lost during convalescence, indicating that antitoxin had not been formed in response to the infectious process.

The serum antistreptolysin titer was measured on the second day of the illness and during convalescence. There was no correlation between the initial level of this antibody and the nature and severity of the clinical disease. The average final titer was somewhat higher in the more severely ill patients, but such an observation is without meaning unless it is correlated with the initial titer, as has been discussed elsewhere.<sup>11</sup> The ratio,  $\frac{\text{maximum titer}}{\text{initial titer}}$ , is a convenient value

*Low Grade Infection*—The clinical course of infection by type 1 hemolytic streptococci, as observed during a food-borne epidemic of sore throat, has been described and the great variation in the clinical course of the disease emphasized. Serious nonsuppurative complications frequently are sequelae of acute streptococcal disease of the respiratory tract, and, because it is believed that these processes may follow even the mildest infection, it is worth while to describe in greater detail the nature of the disease observed in 11 of the study group in whom the temperature was never greater than 99 F. The essential data are presented in table 2.

Malaise was minimal in all of these men, but definite subjective sore throat was present in 6. Exudate and/or adenitis of the cervical lymph nodes was discovered on physical examination of 7 men, including 2 whose throats were not subjectively sore. Symptoms were lacking, and

TABLE 2—Summary of Clinical, Clinicopathologic and Immunologic Observations on Eleven Men Who Became Carriers of Type 1 Hemolytic Streptococci and in Whom Minimal Systemic Reaction Occurred

Patient	Maximum Temperature	Subjective Sore Throat	Tonsillar Exudate	Tender Cervical Adenitis	Total Leukocyte Count $\times 1,000$		Erythrocyte Sedimentation Rate, Mm /Hr		Antistreptolysin Titer		
					Before Infection	Maximum	Before Infection	Maximum	Onset Infection, Units/Cc	Maximum,† Units/Cc	Fold Increase
1	99	Yes	++	++	5	8	3	19	50	125	2.5
2	99	Yes	+	0	5	10	2	11	50	50	0.0
3	99	No	+	0	10	10	15	63	50	100	2.0
4	99	Yes	0	+	9	15	1	7	50	125	2.5
5	99	Yes	0	++	7	10	2	1	50	166	3.3
6	99	No	++	0	9	12	4	4	100	100	0.0
7	98.6	Yes	+++	+++	7	12	2	7	10	50	5.0
8	98.6	Yes	0	0	10	11	8	22	166	625	3.7
9	98.6	No	0	0	8	9	1	1	166	166	0.0
10	98.6	No	0	0	12	12	2	2	125	125	0.0
11	98.6	No	0	0	10	18	2	2	50	50	0.0

+ indicates minimal exudate or adenitis, ++, definite easily recognizable exudate or moderately severe adenitis, +++, very large amounts of exudate

which expresses this relationship. A ratio of 1.5 indicates that a significant antibody response has ensued.

Such an increase in circulating antistreptolysin occurred in 66 per cent of the 35 men who became carriers of type 1 organisms and was slightly greater in magnitude and frequency in severely ill patients. It was also observed after infection associated with no fever or with only a slight febrile reaction. Exudate and adenitis were completely absent in 3, and minimal in 4, in which an antibody response was discovered. Four patients were febrile, and leukocytosis was demonstrated in each.

Four other febrile patients failed to exhibit an antistreptolysin response. Tonsillar exudate and cervical adenitis were minimal but definite in 3 and extensive in the fourth. A significant elevation in the leukocyte count and erythrocyte sedimentation rate was observed in 3.

the physical examinations simultaneously revealed nothing significant in only 3 cases.

The tissue reaction to infection, as measured by the increase in total leukocyte count and erythrocyte sedimentation rate, was minimal in this group of low grade infections. The latter value was elevated for 3 patients, for 1 presenting practically no other signs of infection, to an extreme degree.

A significant increase in the serum antistreptolysin titer occurred during convalescence in 6 cases, and in 2 others there were definite clinical signs of infection. Clinical and/or immunologic evidence of tissue reaction to the epidemic streptococcus was lacking in only 3 of the whole group of 35 who became carriers, and a sharp increase in the total leukocyte count occurred in 1 of the latter.

*Complications*—Suppurative and nonsuppurative complications were notably infrequent in

men infected during the outbreak. It is particularly important that rheumatic fever was never a sequel to the disease, although more than 250 infections were recognized clinically throughout the hospital.

*Remission*—Several hundred patients were resident in the hospital at the time of the epidemic, of whom 60 (in three wards) had group A hemolytic streptococcus sore throat due to a variety of serologic types. These patients were in various stages of convalescence and had previously been under observation. Forty-four were adequately studied after the epidemic, the others having been discharged from the hospital. Type 1 streptococci were isolated from the throats of 11 in whom this type had not previously been present. Sore throat and cervical adenitis, but not exudate, were noted in 3 of this small group. In 4 other patients an elevation in the erythrocyte sedimentation rate followed exposure to the epidemic streptococci.

Type 1 streptococci were never recovered from the nasopharynxes of 33 patients in the postepidemic period. This does not establish the fact that they had not gained lodgment there, since most of these men were already carriers of a different type and the selective isolation of a new strain under these circumstances is difficult. The patients were, however, exposed to reinfection. A slight increase in temperature occurred in 3, in association with sore throat in 2. Cervical adenitis developed in none. In spite of these minimal clinical signs, an increase in total leukocyte count and/or erythrocyte sedimentation rate was demonstrated in 15 during the postepidemic period.

Minimal signs of infection were noted in only 6 of this group of 44 patients, but laboratory evidence of a tissue reaction to the different type of streptococcus in the absence of clinically demonstrable disease was discovered in 19. These observations assume greater significance when it is realized that definite, clinically recognizable hemolytic streptococcal sore throat developed in 50 to 60 per cent of the remaining hospital patients who had not previously undergone an infection by group A streptococci.

#### COMMENT

Information has been accumulating for more than fifteen years<sup>5</sup> which has indicated that group A hemolytic streptococcus infection of the

respiratory tract is intimately associated with the development of rheumatic fever. Recent definitive studies<sup>6</sup> show that this serious disorder occurs only as a sequel to infection by these organisms and, furthermore, that a potentially serious nonarthritic continuing disease process is initiated by such infection in many persons. It has, therefore, become important to describe the natural history of hemolytic streptococcal disease in detail. Comparative studies of natural infection are difficult, because the size of the infecting dose and strain of the etiologic agent may vary from case to case. This paper summarizes the results of clinical and laboratory observations of a food-borne epidemic of type 1 hemolytic streptococcus sore throat in a military hospital. Under these circumstances it is reasonable to assume that the same organism, ingested by each man in approximately comparable numbers, was responsible for the outbreak.

Fifty-eight men, of whom 35 became carriers of the epidemic type, were studied clinically and bacteriologically. The others may not have consumed the contaminated food, but another factor appears to have been at work. Tonsillectomy had been performed approximately 9 times as frequently among those men who did not become carriers as among those who did. This observation is to be contrasted with those made in the study of another large group of cases, in which the infection was caused by a variety of types of the organism and in which the absence of tonsils was not found to interfere with the development of streptococcal sore throat.<sup>7</sup> Bloomfield<sup>8</sup> has previously noted the protection offered by tonsillectomy against infection by streptococci, but the observations recorded here indicate that the nature and type of the etiologic agent must be carefully defined before such studies can be compared and evaluated.

The clinical disease which occurred among the 35 men who became carriers of the epidemic type varied greatly, and the cases could be divided into groups on the basis of maximum temperature. When the temperature reached 101 F or more, the disease was usually "typical," in that sore throat, tonsillar exudate, adenitis involving the anterior cervical lymph nodes, with tender-

6 Rantz, L. A., Boisvert, P. J., and Spink, W. W. Etiology and Pathogenesis of Rheumatic Fever, *Arch Int Med* 76 131 (Sept) 1945.

7 Rantz, L. A., Spink, W. W., and Boisvert, P. J. Hemolytic Streptococcal Sore Throat. The Acute Disease, to be published.

8 Bloomfield, A. L., and Felty, A. R. Bacteriologic Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility, *Arch Int Med* 32 483 (Oct) 1923.

5 Paul, J. R., and others. The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, New York, Metropolitan Life Insurance Company for the American Heart Association, 1943.

ness, leukocytosis and increased erythrocyte sedimentation rate were observed. Either tonsillar exudate or cervical lymphadenitis or both, was present in all but 2 of the febrile patients but was discovered in several only by careful examination by experienced clinicians. It is probably fair to state that in ordinary practice the diagnosis of streptococcic sore throat would not have been made on clinical grounds for at least 25 per cent of this group of definitely infected patients. In the absence of special laboratory and bacteriologic study, these men would usually have been supposed to suffer from a "virus" type of infection of the respiratory tract.

Eleven patients in whom the maximum temperature was never more than 99 F were of great importance. Generalized symptoms of an acute infection were almost completely lacking in these men. In military practice they would not have been removed from duty and in civilian life would not, in all probability, have consulted a physician. Definite clinical evidence of infection was present in 8, and in several the total leukocyte count or erythrocyte sedimentation rate was increased.

The serum antistreptolysin titer was measured at the onset of the acute illness and during convalescence. A significant increase in titer was frequently observed, even though the systemic reaction was slight or the physical signs usually associated with hemolytic streptococcus sore throat were minimal or absent. An antibody response did not occur after some of the most severe and typical infections.

The foregoing observations demonstrate that nearly all the persons who became carriers of the epidemic type of group A streptococci after exposure to infected food were infected and that the syndrome usually designated as follicular tonsillitis was frequently observed. There were, however, many mild and atypical cases in which the correct etiologic agent would not usually have been recognized in the absence of special laboratory study. It is probable that just such atypical diseases of the respiratory tract as these, occurring as the result of non-food-borne natural infection, have been responsible for the initiation of the many instances of rheumatic fever and other types of poststreptococcic nonsuppurative disorders in which a past history of infection by these organisms has not been obtained.

The complete suppression of tissue invasion by hemolytic streptococci must be the goal of all control measures for the prevention of late complications. Their eradication by technics for the treatment of the acute phase of the disease or the respiratory tract must fail, because

many infected persons will not become sufficiently ill to require medical care and others will fail to present signs permitting the clinical recognition of the cause of the disease.

Suppurative and nonsuppurative complications, as sequelae to the disease caused by the epidemic streptococci, were found to be consistently absent, in contrast with the results of study of similar infections by a variety of other types during the same season.<sup>6</sup> This absence of complications is probably the result of the failure of the infecting strain to elaborate some essential toxin or other bacterial product. Similarly, this organism did not induce the formation of a rash in persons with positive Dick reactions or stimulate an antifibrinolysin response. In spite of these deficiencies, the strain was highly invasive, only 3 of the 35 men who became carriers having escaped infection as determined by clinical and immunologic observations.

A number of men previously infected by other types of group A streptococci were hospitalized at the time of the epidemic and were exposed to reinfection. Study of their cases revealed a curious phenomenon that deserves special consideration. None of these men reacted to the presence of the new type with more than minimal clinical signs of infection, yet in nearly one half significant increase in the total leukocyte count and/or erythrocyte sedimentation rate was demonstrated. Previous infection by another type had prevented the usual clinical signs of hemolytic streptococcus sore throat from developing but had not prevented a tissue reaction as the result of invasion of the throat by the epidemic type.

Evidence has been presented elsewhere<sup>6</sup> which strongly suggests that reinfection by new types of group A streptococci may be important in the pathogenesis of rheumatic fever and the other phenomena following streptococcic infections. The facts just stated suggest that such reinfection may often be unrecognizable clinically and may be demonstrable only by detailed bacteriologic study of the flora of the throat and by laboratory tests.

The results of this study show that the clinical signs and the course of hemolytic streptococcus disease of the respiratory tract may be highly variable and that the amount of tissue reaction and degree of antibody response is not well correlated with the severity of the illness. The nature of the disease is greatly altered by preceding infection by strains of another type.

It is hoped that these observations may focus attention on the large group of cases of mild and

atypical streptococcic infection and on their potential importance in the causation of rheumatic fever and other disorders now believed to be sequelae to infection by these organisms

#### SUMMARY AND CONCLUSIONS

A large number of men simultaneously exposed to infection by group A streptococci were studied

Tonsillectomy appeared to offer considerable protection against infection by the epidemic type

The disease produced in different patients varied greatly in its severity and in the amount of tissue reaction demonstrated

Many examples of mild or clinically atypical disease were observed which would not usually be recognized as instances of streptococcic infection

Previous infection by another type of group A streptococcus profoundly modified the nature and course of the disease produced by the epidemic type

# SMALL ADENOMAS OF THE ADRENAL CORTEX IN HYPERTENSION AND DIABETES

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The principal observations generally reported concerning persons with tumors of the adrenal cortex consist of obesity, purple striae of the skin, acne, polycythemia, osteoporosis, imbalance of plasma electrolytes, diabetes, hypertension and genital dystrophy. These signs and symptoms have been observed in persons with adenomas and hyperplasias as well as in those with carcinomas of the adrenal cortex, and the total picture is usually referred to as Cushing's disease or adrenogenital syndrome. In general, even the benign tumors which produce this clinical entity occupy a large portion of the adrenal gland. There are, in addition, as Kepler and Keating<sup>1</sup> have pointed out, a large number of small cortical adenomas which are encountered incidentally in the course of routine autopsies in persons in whom there was no apparent clinical evidence of endocrine disease during life. The investigations presented here were undertaken in order to determine whether or not an examination of the clinical and pathologic data, in retrospect, would show the presence of certain endocrinologic disturbances not noted during the life of those patients. This report contains a survey of 131 cases of small adenomas of the adrenal cortex encountered in the course of 9,000 consecutive necropsies.

## RESULTS

*Incidence, Age and Sex Distribution*—The incidence of cortical adenomas in this series, 131

The investigations were aided by a grant from the David May-Florence G May Fund.

This article is based entirely on investigations conducted at Snodgrass Laboratory, City Hospital and Laboratory of the Jewish Hospital in St. Louis.

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<sup>1</sup> Kepler, E J, and Keating, F R, Jr. Diseases of the Adrenal Glands. Tumors of the Adrenal Cortex, Diseases of the Adrenal Medulla and Allied Disturbances, Arch Int Med 68 1010-1036 (Nov) 1941.

cases in 9,000 autopsies, is 1.45 per cent. However, since these necropsies were performed by many different persons, it is probable that there were many instances in which small tumors were missed or not recorded and that the actual frequency with which these tumors occur probably is slightly higher. Seventy-one of the adenomas (54.2 per cent) occurred in males, while 60

TABLE 1—A Comparison of the Age Distribution in One Hundred and Thirty-One Cases of Adenomas of the Adrenal Cortex with That in Nine Thousand Autopsies

Age by Decades	Age Distribution in 131 Cases of Cortical Adenoma		Age Distribution in 9,000 Consecutive Autopsies	
	Number	Per Cent	Number	Per Cent
Premature	0	0	270	3.0
0-9	1	0.8	675	7.5
10-19	0	0	234	2.6
20-29	0	0	441	4.9
30-39	2	1.5	729	8.1
40-49	18	13.7	1,125	12.5
50-59	34	26.0	1,719	19.1
60-69	43	32.8	1,935	21.5
70-79	18	13.7	1,449	16.1
80-89	15	11.5	387	4.3
90-100	0	0	36	0.4
Total	131	100.0	9,000	100.0

(45.8 per cent) were observed in females. Since the male to female ratio in our series is about 2:1, the incidence of adrenal adenomas in relation to sex is 2 per cent in females and 1.2 per cent in males.

A comparison of the age distribution in the 9,000 necropsies with that in the 131 cases of adenomas of the adrenal cortex is shown in table 1. It can be seen that only 3 patients with adenomas were found below the age of 40 years, after which there was a gradual rise in the incidence until a peak was reached in the decade between 60 and 69 years, this was followed by a decline in the next two decades. While these figures alone might imply a gradual rise in the incidence of these tumors, with a maximum being reached during the seventh decade, a comparison with the age distribution in autopsies in general shows that both have a similar curve.

However, the possibility that there is such an increase in incidence with increasing age cannot be definitely eliminated by this comparison

*Anatomic Characteristics*—As just stated, we studied small adenomas which were incidentally found at necropsy. These varied from small microscopic nodules (3 instances) to tumors approximately 6 cm in diameter (1 instance). The average size was about 1 cm in diameter. Representative gross sections are shown in figure 1.

In 68 instances there was a record of the side on which the tumor was found. In 21 cases (31 per cent) it was found on the right side and in 34 cases (50 per cent) on the left side, while there were 13 instances (19 per cent) in which bilateral adenomas were observed. Multiple nodules in a single gland were found in only 2 specimens.

tissue adjacent to the tumor. The adenoma frequently appeared paler than the neighboring cortical tissue when the section was examined with the naked eye or the hand lens. The second type of cortical cell generally showed a centrally located nucleus more vesicular than that seen in the first type, and the cytoplasm was either homogeneously eosinophilic or contained finely dispersed lipid droplets. The relative numbers of each cell type varied in different tumors, but, in general, the first type predominated, although occasionally they were present in approximately equal numbers. In figure 2 there is shown a tumor in which the vacuolated type of cell was predominant, but islands of smaller solid cells were also present, and these are indicated by arrows.

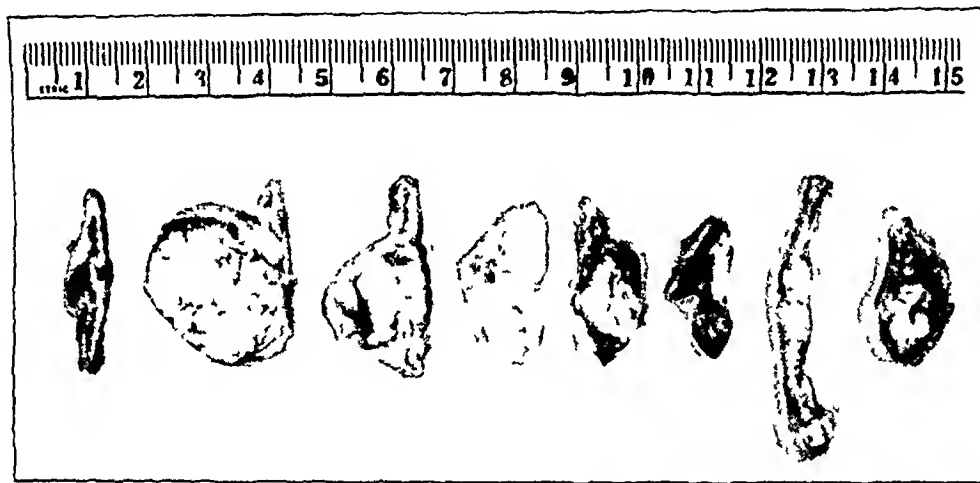


Fig 1—Gross appearance of cortical adenomas on cross section. (Specimen on the extreme left is a cross section of a normal adrenal gland)

Microscopically these nodules were sharply demarcated but not definitely encapsulated. In no instance was there any evidence of malignant invasion. The general morphologic structure of the individual cells was essentially similar to that of the cells forming the cords of the adrenal cortex. There was usually some distortion in the cellular outline, apparently due to the resistance of neighboring structures to the new growth. The cordlike arrangement of the cells had undergone varying degrees of distortion. In some areas the cords, although distinctly visible, appeared angulated, arched and of varying length. The cords failed to arrange themselves in parallel rows. In other areas the cord arrangement was entirely obliterated. The cortical cells composing the adenomas were of two types. The first of these contained either a centrally or eccentrically placed hyperchromatic nucleus and cytoplasm filled with medium-sized and large-sized lipid vacuoles. The lipid vacuoles were usually larger than those seen in the cells of the normal cortical

#### DISEASES ASSOCIATED WITH SMALL ADENOMAS OF THE ADRENAL CORTEX

A survey of the clinical data showed hypertension and diabetes to be the only diseases occurring with sufficient frequency to warrant an analysis of their relation to these small tumors of the adrenal cortex. Accordingly, we are presenting the data used to determine whether or not these diseases occurred with significantly greater frequency in persons with cortical adenomas than in the general group of autopsy

1 *Hypertension*—Both clinical and necropsy data were used in order to determine the presence of hypertension. The determination of clinical evidence of hypertension was patterned according to certain of the criteria used by Master, Marks and Dack,<sup>2</sup> whose data we have also

2 Master, A. M., Marks, H. H., and Dack, S. Hypertension in People over Forty, *J. A. M. A.* **121**: 1251-1256 (April 17) 1943.

used to compare with certain of our observations. Two divisions of the clinical group were made, (a) those patients with a blood pressure of 140 systolic and 90 diastolic or over and (b) those with a diastolic pressure of 95 or over. The pathologic evidence for the existence of hypertension was the presence of cardiac hypertrophy (weight of the heart in excess of 350 Gm) in the absence of a valvular or myocardial lesion other than infarction due to coronary occlusion. No attempt was made to compare this evidence of hypertension with the sphygmomanometric data recorded in the clinical history of the 9,000 subjects studied by autopsy. Many of these were seen for the first time when they were dying, when the evaluation of the preexisting hypertension was extremely difficult. Instead, our autopsy data are compared with the data on

decades, it may be noted that there was definitely an increase after the age of 60 as compared with previous decades, although there were some minor fluctuations which were probably not significant but which were always above the percentages found in earlier decades.

As far as the 131 patients with cortical adenomas are concerned, there were 100 for whom complete clinical data were available for comparison with the necropsy observations. Seventy of these showed evidence of some degree of hypertension, while for 30 there were no clinical and pathologic evidences. In addition, there were 22 others in whom definite cardiac hypertrophy was present but for whom there were insufficient clinical data to determine the presence of a hypertensive state. Finally, there were 9 subjects who had to be eliminated because of valvular lesions

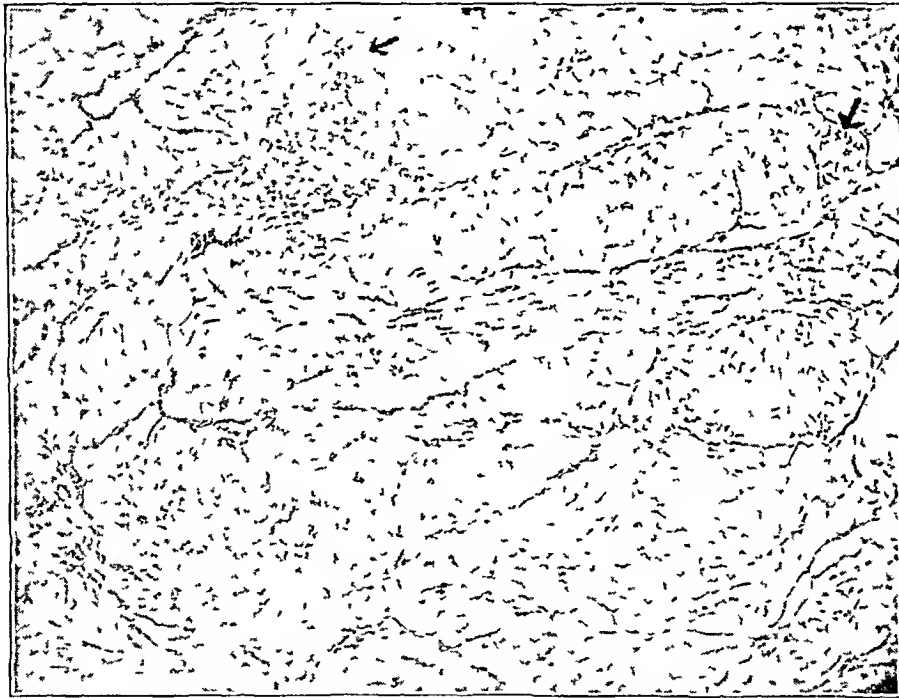


Fig 2—Photomicrograph showing large areas composed of the vacuolated type of cell and smaller areas indicated by arrows, composed of the more solid type of cell ( $\times 100$ )

living persons reported by Master, Marks and Dack and covering approximately 15,000 patients. This comparison is shown in table 2.

From the data of Master, Marks and Dack<sup>2</sup> it was determined that when the less critical criterion for the presence of hypertension was used (blood pressure 140 systolic and 90 diastolic), over half of the patients examined showed evidence of hypertension. On the other hand, when the more critical basis was employed (diastolic tension over 95), the percentage of those with hypertension fell to 22.4. The latter is more in agreement with the figure obtained by us on the basis of cardiac hypertrophy, namely 13.9 per cent. As to the percentages in various

which produced a cardiac hypertrophy and abnormality in blood pressure.

The data showed a greater increase in the incidence of hypertension in persons with adrenal adenomas than that in the general group examined at autopsy, by whatever criteria were used. If the less critical criterion (blood pressure 140 systolic and 90 diastolic) is used, there is an incidence of 70 per cent in the group with adenomas, as compared with 54.9 per cent in the clinical group presented by Master, Marks and Dack. If a diastolic pressure in excess of 95 is used as the basis, the group with cortical adenomas shows an incidence of 42 per cent, as compared with 22.4 per cent in the clinical group.

Finally, if a comparison is made on the basis of observations at autopsy, the group with adenomas shows an incidence of 72.9 per cent, as compared with 13.9 per cent in the general group examined at autopsy. It should be noted that in 96 per cent of the persons with adrenal adenomas having a blood pressure of 140 systolic and 90 diastolic or over there was evidence of cardiac hypertrophy at autopsy. A further breakdown of the data for the 100 persons with cortical adenomas according to the degree of hypertension shows that there were 70 with a blood pressure of 140 systolic and 90 diastolic or over, 57 with 150 systolic and 90 diastolic or over and 35 with a tension of 150 systolic and 100 diastolic or over. Of the 13 with a blood pressure between 140 systolic and 90 diastolic and 150

Finally, in presenting the data we should emphasize that there were 14 hypertensive persons among the 92 persons with adenomas of the adrenal cortex (15.2 per cent) in whom there was also a renal lesion to which the hypertension might possibly be attributed.

2 *Diabetes*—In the analysis of the data it was observed that diabetes also occurred frequently in persons with cortical adenomas. It was noted that there were 270 persons with diabetes in the general group of 9,000 examined by autopsy, an incidence of 3 per cent. On the other hand, among the 131 persons with cortical adenomas there were 21 with proved diabetes, or an incidence of 16 per cent. Of these 21 persons, 16 were also in the group with both clinical and pathologic evidence of hypertension.

TABLE 2—A Comparison of the Incidence of Hypertension in a Clinical Group with That in an Autopsy Group and a Group with Adenomas of the Adrenal Cortex

Group	Number of Cases	Number of Hypertensive Persons	Percentage of Hypertensive Persons	Age of Hypertensive Persons (Percentage by Decade)†					
				0-39	40-49	50-59	60-69	70-79	80-100
1 Clinical group *									
a Blood pressure 140/90 or over	14,849	8,148	54.9		36.6	55.3	71.4	79.2	81.5
b Diastolic pressure 95 or over	14,849	3,320	22.4		11.6	21.9	27.7	33.4	30.7
2 Autopsy group									
Cardiac hypertrophy	9,000	1,254	13.9	4.1	17.5	16.2	23.0	19.7	22.6
3 Adrenal adenoma group									
a Blood pressure 140/90 or over	100	70	70.0	50.0	42.9	68.0	78.8	91.8	64.3
b Diastolic pressure 95 or over	100	42	42.0	0	42.9	52.0	42.4	41.7	28.6
c Cardiac hypertrophy at autopsy	122	89	72.9	69.6	50.0	72.1	78.0	88.8	66.6

\* The clinical group was obtained by combining the data for the two sexes in the article by Masters, Marks and Dack.<sup>2</sup>  
 † These figures were obtained by dividing the number of hypertensive persons in a given decade by the total number of persons (normal plus hypertensive) for that decade.

systolic and 90 diastolic, only 3 failed to show evidence of cardiac hypertrophy. As far as the percentages at various decades are concerned, the relation in the group with adrenal adenomas is essentially similar to that seen in the general clinical and autopsy groups. The apparent exception is in group 3 B (table 2), but this is probably not significant and may be due to the relatively small number of patients.

When the hypertensive persons are grouped according to decade (table 3), it can be seen that the greatest incidence in all groups generally lies between the ages of 40 and 69. More specifically, it may be noted that in the four groups comprising this study the maximum number is reached in the seventh decade of life in three of them and in the sixth decade in one. In the clinical group of Master, Marks and Dack, both subclassifications show a maximum between the ages of 40 and 49. While the incidence of hypertension is apparently higher after the age of 60 in all groups, including those with adenomas of the adrenal cortex, the greatest incidence in a given decade is reached before the age of 70

and 3 others in the group with cardiac hypertrophy without sufficient clinical evidence of an elevation in blood pressure, while only 2 were in the unclassified group. Thus, as in the case of

TABLE 3—A Comparison of the Age Distribution of the Hypertensive Persons in Various Groups

	Percentage of the Total Number of Hypertensive Persons					
	0-39	40-49	50-59	60-69	70-79	80-100
1 Clinical group						
a Blood pressure 140/90 or over		28.0	25.2	25.5	15.6	5.7
b Diastolic pressure 95 or over		30.0	24.5	24.3	16.1	5.0
2 Autopsy group						
Cardiac hypertrophy	6.9	14.1	19.8	31.8	20.4	7.0
3 Adrenal adenoma group						
a Blood pressure 140/90 or over	1.4	8.6	24.3	37.1	15.7	12.9
b Diastolic pressure 95 or over		17.1	31.4	28.6	14.3	8.6
c Hypertrophy of heart	2.2	9.0	22.5	35.9	19.1	11.2

hypertension, a comparison of the incidence of diabetes in the general autopsy group and in the group with adrenal adenomas shows an approxi-

mate<sup>3</sup> would increase in the incidence in the over the former. In addition, in almost all instances in which diabetes was present in association with an adenoma evidence of hypertension was also present.

## COMMENT

The results presented here show that the incidence of adenomas of the adrenal cortex was at least 1.45 per cent in 9,000 autopsies and that there is no significant difference in incidence between males (1.2 per cent) and females (2 per cent). There appears to be an increase in incidence up to the decade of 60 to 69 years and then a gradual decline, although it is possible that this is only a reflection of the age distribution in the autopsies as a whole.

Anatomically the tumors vary from small microscopic nodules to growths which reach a diameter of about 6 cm, the average being about 1 cm in diameter. As stated, they are composed of two principal types of cells, the first with large lipid-containing vacuoles occupying the cytoplasmic area and the second with finely granular or solid cytoplasm. Ewing<sup>3</sup> has designated these small tumors as focal hyperplasias, in contradistinction to the larger tumors, which are true adenomas. According to him, the former may usually be distinguished from the latter in that the structure reproduces cortical zones whereas true adenomas have a typical neoplastic structure. The so-called true adenomas are believed to be relatively rare by Kelynack,<sup>4</sup> who found only 3 in 1,500 autopsies. As stated, the architectural pattern in a single tumor may vary from slight distortion of the cords to their complete obliteration. Thus there is probably no sharp distinction between focal hyperplasia and true adenoma on an anatomic basis.

Likewise, the functional distinction between small tumors of the adrenal cortex of the so-called clinically indifferent type and larger tumors which are associated with endocrinologic disorders is a relative one, since, as we have shown, even in association with the former hypertension and diabetes occur approximately five times as frequently as in the general autopsy group, and in many cases both diseases occur in the same person.

There exists considerable clinical and experimental evidence of the relation of the adrenal cortical hormones to hypertension and diabetes, but a careful evaluation of the clinical features is frequently difficult, particularly in the case of

hypertension. There has often arisen some question as to the reliability of certain of the clinical criteria for the determination of the presence of this disease. Wilburne and Ceccolini<sup>5</sup> have recently presented several reasons for widely discrepant figures on the incidence of hypertension, namely, (1) a lack of agreement as to what blood pressure levels constitute arterial hypertension, (2) lack of rest periods during testing and (3) insufficient precautions for the elimination of such influences as dietary and psychic factors. Recently Master, Marks and Dack<sup>2</sup> stated that they consider the estimated incidence of hypertension in persons over 40 to be too high, and we have shown here that certain of their figures are considerably higher than those derived from observations at necropsy. Proof of hypertension by autopsy, as manifested by cardiac hypertrophy in the absence of valvular lesions, myocardial disease or congenital defects, offers the most reliable criterion when it can be employed.

Oppenheimer and Fishberg<sup>6</sup> have reviewed the literature concerning the association of adrenal cortical tumors with hypertension since it was first observed by Neusser,<sup>7</sup> in 1898, and have presented a number of additional cases. More recently Rinehart, Williams and Cappeller<sup>8</sup> have studied 26 cases of essential hypertension and have observed nodular or adenomatous hyperplasia in the adrenal cortex in a high percentage of these cases. On the other hand, Dempsey<sup>9</sup> has reported that in patients with essential hypertension the average weight of the adrenal gland was not significantly higher than in nonhypertensive control patients. He studied a total of 102 patients, of whom only 19 were classified as being definitely hypertensive. In all of this group there were only 9 with cortical adenomas, and of these only 3 were persons with essential hypertension. From this small number it was concluded that nodular or adenomatous hyperplasia of the adrenal cortex was not regularly found in association with essential

5 Wilburne, M., and Ceccolini, E. M. A Note on the Incidence of Arterial Hypertension in 25,000 Army Examinees, *Army M. Bull.*, 1943, no. 68, pp. 118-125.

6 Oppenheimer, B. S., and Fishberg, A. M. The Association of Hypertension with Suprarenal Tumors, *Arch. Int. Med.* **34**: 631-644 (Nov.) 1924.

7 Neusser, E., in Nothnagel, C. W. H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1898, pp. 18 and 71.

8 Rinehart, J. F., Williams, O. O., and Cappeller, W. S. Adenomatous Hyperplasia of the Adrenal Cortex Associated with Essential Hypertension, *Arch. Path.* **32**: 169-177 (Aug.) 1941.

9 Dempsey, W. S. The Adrenal Cortex in Essential Hypertension, *Arch. Path.* **34**: 1031-1034 (Dec.) 1942.

3 Ewing, J. *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1941, pp. 830-831.

4 Kelynack, cited by Ewing.<sup>3</sup>

hypertension and that it occurred with considerable frequency in nonhypertensive persons. In general, each investigator has dealt with small numbers of cases, and the relation of these tumors to the total picture of the cause of hypertension could not be accurately evaluated. Recently Castleman and Smithwick<sup>10</sup> examined by biopsy the kidneys of 100 patients with clinical hypertension and observed that in more than half of them evidence of renal vascular disease was inadequate. The small number of patients with renal lesions in this group of persons with adrenal adenomas similarly indicates that hypertension cannot always be accounted for on the basis of pathologic changes in the kidneys. It should be noted further that Castleman and Smithwick observed that 6 of the 100 patients studied were found to have cortical adenomas. This incidence is in essential agreement with that of our much larger series, in which 89 of a total of 1,254 hypertensive patients (7.4 per cent) had this type of tumor. Additional evidence showing a relation between the adrenal cortical hormones and hypertension is found in the experiments of Helfrich, Cassels and Cole,<sup>11</sup> who observed that cortical extract is effective in preventing the usual fall in blood pressure when shock is produced, and in the observation by Loeb<sup>12</sup> that in 4 patients receiving desoxycorticosterone for the treatment of Addison's disease hypertension developed. In Loeb's cases it was not known whether or not these patients had underlying hypertensive disease masked by the Addison disease. The ability of desoxycorticosterone acetate to elevate the blood pressure to hypertensive levels is also demonstrated in the experiments of Rodbard and Freed.<sup>13</sup> These investigators showed that the injection of this substance into previously hypertensive dogs caused pulmonary edema to develop, while in previously nonhypertensive dogs an elevation in blood pressure was produced which persisted for variable periods after cessation of injections.

Certain experimental observations suggest the possibility that the adrenal hormones (1) may

render a person more sensitive to changes in the kidneys which would lead to increased renin production. The former possibility is suggested by the experiments of Williams, Diaz, Burch and Harrison,<sup>14</sup> who found that adrenalectomized rats are noticeably less sensitive to renin than normal rats. The latter possibility is presented in the experiments of Selye and Hall.<sup>15</sup> These investigators observed that large doses of desoxycorticosterone acetate produced definite renal changes in fowl and dogs similar to those seen in human patients with nephrosclerosis. These changes were more readily obtained in fowl, but could also be produced in mammals, although it is probable that the refractory state is much longer in the latter than in birds. Opposed to these interpretations is our observation that in only 14 of the 92 patients with adrenal cortical tumors and evidence of hypertension (15.2 per cent) was there any degree of renal damage to which the hypertension might be attributed. It seems more likely that there is a direct effect of the cortical hormones on vascular tone, as indicated by the experiments on prevention of shock and that the renal damage observed by Selye and Hall<sup>15</sup> is due to a toxic effect of large doses of desoxycorticosterone.

The role of the adrenal hormones in the production of a hyperglycemic state has been amply reviewed by Britton and Silvette,<sup>16</sup> Soskin,<sup>17</sup> Kendall,<sup>18</sup> Evans<sup>19</sup> and Long, Katzin and Fry.<sup>20</sup> Suffice it to state here that it is now generally agreed that certain of the adrenal cortical hormones increase the rate of glycconeogenesis and

14 Williams, J. R., Diaz, J. T., Burch, J. C., and Harrison, T. R. The Relation of the Adrenal Glands to the Action of the Renal Ppressor Substance, *Am J M Sc* **198** 212-219, 1939.

15 Selye, H., and Hall, C. E. Pathologic Changes Induced in Various Species by Overdosage with Desoxycorticosterone, *Arch Path* **36** 19-31 (July) 1943.

16 Britton, S. W., and Silvette, H. The Adrenal Cortex and Carbohydrate Metabolism, in *Cold Spring Harbor Symposia on Quantitative Biology*, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, pp. 357-359.

17 Soskin, S. Metabolic Functions of the Endocrine Glands, in Luck, J. M. *Annual Review of Physiology*, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, pp. 543-572.

18 Kendall, E. C. The Function of the Adrenal Cortex, in *Glandular Physiology and Therapy*, Chicago, American Medical Association, 1942, pp. 273-286.

19 Evans, G. The Adrenal Cortex and Endogenous Carbohydrate Formation, *Am J Physiol* **114** 297-308, 1936.

20 Long, C. N. H., Katzin, B., and Fry, E. G. The Adrenal Cortex and Carbohydrate Metabolism, *Endocrinology* **26** 309-344, 1940.

10 Castleman, B., and Smithwick, R. H. The Relation of Vascular Disease to the Hypertensive State, Based on a Study of Renal Biopsies from One Hundred Hypertensive Patients, *J A M A* **121** 1256-1261 (April 17) 1943.

11 Helfrich, L. S., Cassels, W. H., and Cole, W. H. Cortical Extract in the Treatment of Shock. Preliminary Report, *Am J Surg* **55** 410-426, 1942.

12 Loeb, R. F. Adrenal Cortex Insufficiency, in *Glandular Physiology and Therapy*, Chicago, American Medical Association, 1942, pp. 287-305.

13 Rodbard, S., and Freed, S. C. The Effect of Desoxycorticosterone Acetate on the Blood Pressure of the Dog, *Endocrinology* **30** 365-368, 1942.

by <sup>Ch</sup> <sup>ally</sup> means increase the blood sugar level. It has been observed by Lukens, Flippin and Thigpen<sup>21</sup> that of 55 patients with carcinoma, hypernephroma, adenoma or hyperplasia of the adrenal cortex 27 (49 per cent) showed an impaired sugar tolerance compatible with a diagnosis of diabetes. The frequent presence of diabetes in association with cancers or large benign tumors of the adrenal cortex has already been mentioned.

In view of the fact that of the 21 patients with adrenal cortical adenomas and diabetes 19 also showed either clinical or pathologic evidence of hypertension, it is of interest to speculate whether these tumors elaborate a single hormone or produce the multiplicity of hormones in a manner similar to the normal adrenal cortex, but perhaps in excessive amounts. In the abundant literature on adrenal cortical hormones one finds evidence that desoxycorticosterone affects primarily salt and water metabolism, whereas corticosterone and its derivatives affect primarily sugar metabolism through glyconeogenesis, as already stated, and the amorphous fraction affects renal function. However, there may be some overlapping in these processes. Clinically, desoxycorticosterone is effective in raising the blood pressure of patients in shock, and it is also this substance which is suspected of producing hypertension in patients treated for Addison's disease, but it is relatively ineffective in raising the blood sugar level. This evidence would lead one to conclude that these tumors are probably able to elaborate more than one hormone and in this respect function in a manner similar to the normal adrenal cortex.

There remains, finally, to discuss the physiologic roles of the two types of cells noted in histologic sections. In 1942, in underfeeding experiments on guinea pigs, it was pointed out by Blumenthal and Loeb<sup>22</sup> that the degree of mitotic activity in the adrenal cortex is in inverse ratio to the number of lipid vacuoles present in the fasciculate cells. This principle has been observed to hold true by Blumenthal in a more extensive series of as yet unpublished experiments on guinea pigs. It has also been noted by

Dosne and Dalton,<sup>23</sup> as well as by Selye,<sup>24</sup> that the amount of cortical lipid, as demonstrated by either a sudan stain or osmium tetroxide, definitely decreases as the adrenal gland enlarges with increased activity. More recently Sarason<sup>25</sup> has observed a decrease in cortical lipids in human beings with overwhelming infection and cachexia, as well as in rats under certain experimental conditions. In a second paper the same investigator<sup>26</sup> again observed a cortical enlargement associated with decreased amount of lipid in inflammatory diseases, cachexia, pemphigus and protracted emesis. This evidence suggests that under these conditions there occurs a discharge of lipid into the circulation and the cytoplasm of cortical cells changes from the vacuolated to the more solid or granular state. However, Sarason was unable to explain the observation that in hypertension there was a cortical enlargement associated with an increased amount of lipid.

It has recently been shown by Sayers, Sayers, White and Long<sup>27</sup> that 2 mg of pituitary adrenotropic substance produces a distinct lowering of the adrenal cholesterol level in rats three hours after injection, while repeated injections over a period of three days result in an increase in adrenal cholesterol concentration above that of control animals. This experiment may be interpreted as showing that the immediate effect of a stimulus on the adrenal cortex is to release adrenal cortical hormones into the circulation, and it may reasonably be expected that this would be manifested histologically in the non-vacuolated, relatively solid type of cortical cell. Subsequent injections of pituitary adrenotropic substance may result in a condition in which the process of storage of hormones exceeds the output, resulting in an increase in adrenal cholesterol concentration. If subsequent stimuli continue to be strong, as for example in severe cachexia, the solid type of adrenal cell may remain predominant, because the adrenal hormones are probably being discharged as rapidly as they are formed. In interpreting the preponderance of vacuolated cells in the adenomas associated with hypertension, we suggest that there may be a

24 Selye, H. Studies on Adaptation, *Endocrinology* **21** 169-188, 1937.

25 Sarason, E. L. Morphologic Changes in the Rat's Adrenal Cortex Under Various Experimental Conditions, *Arch Path* **35** 373-390 (March) 1943.

26 Sarason, E. L. Adrenal Cortex in Systemic Disease, *Arch Int Med* **71** 702-712 (May) 1943.

27 Sayers, G., Sayers, M. A., White, A., and Long, C. N. H. Effects of Pituitary Adrenotropic Hormone on Cholesterol Content of Rat Adrenal Glands, *Proc Soc Exper Biol & Med* **52** 200-202, 1943.

21 Lukens, F. D. W., Flippin, H. F., and Thigpen, F. M. Adrenal Cortical Adenoma with Absence of the Opposite Adrenal. Report of a Case with Operation and Autopsy, *Am J M Sc* **193** 812-830, 1937.

22 Blumenthal, H. T., and Loeb, L. Two Antagonistic Effects of Underfeeding on Adrenal Cortex of the Guinea Pig, *Am J Path* **18** 615-631, 1942.

23 Dosne, C., and Dalton, A. J. Changes in Lipoid Content of Adrenal Gland of Rat Under Conditions of Activity and Rest, *Anat Rec* **80** 211-217, 1941.

relatively weak but persistent stimulus similar to repeated small injections of pituitary extract in the experimental situation and that, while the storage of lipids exceeds the rate of discharge, the latter may still be greater than that in the normal adrenal cortex. The presence of islets of solid cells in practically every cortical adenoma probably indicates the sites in which there is an active discharge of hormones at the same time that the process of storage is going on in other areas.

#### SUMMARY

The incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies was found to be at least 1.45 per cent. The inci-

dence was 2 per cent in females and 1.2 per cent in males. There appeared to be a gradual increase in age incidence up to the seventh decade, although this may have been only a reflection of the age distribution of the autopsies as a whole.

Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group, and both diseases were frequently present in association with such a tumor in a single person.

The relation of the adrenal hormones to diabetes and hypertension was studied, and hypotheses concerning the possible role of the vacuoles and solid cells comprising the tumors in the production and storage of these hormones were formed.

# PAROXYSMAL HEMOGLOBINURIA DUE TO THE COLD HEMOLYSIN

OBSERVATIONS WITH A REPORT OF A CASE OF ITS OCCURRENCE  
IN AN AERIAL GUNNER

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Hemoglobinemia with resultant hemoglobinuria is exhibited in several varied clinical conditions. Notably these are (a) in a certain percentage of burns, (b) in some severe infectious diseases, including the exanthemas, (c) after extended physical exertion, as is seen in the so-called march hemoglobinuria<sup>1</sup> of the soldier and probably more specifically a myoglobinuria, (d) from organic toxins, such as venom, the deadly mushrooms and favism (a sensitivity reaction)—a disease which might appear in troops in Italy, especially southern Sicily, where the bean *Vicia faba* is plentiful, (e) in poisoning with chemicals such as toluylene diamine, saponin and photodynamic fluorescent hydrocarbons, including sulfonamide drugs and acridine dyes,<sup>2</sup> (f) in blackwater fever sometimes complicating malaria, (g) in some forms of chronic hemolytic anemia known as Marchiafava-Micheli, or nocturnal, hemoglobinuria<sup>3</sup>, (h) in severe cardiac decompensation, (i) from incompatibility in blood transfusions, (j) in reabsorption from internal hemorrhage, and (k) in certain cases of probable syphilis which develop hemoglobinuria in response to the formation and action of a cold hemolysin. Possibly the phenomenon is present also in small degree physiologically, although when hemolysis occurs slowly and is not too great the hemoglobin is readily converted to bilirubin, from which the liver then produces urobilin.<sup>4</sup> Also, up to a certain amount, hemo-

globin passed through the glomeruli is taken up and conserved by the epithelium of the convoluted tubules.<sup>5</sup> A series of experiments for the study of hemoglobinuria<sup>6</sup> produced in dogs would indicate that the renal threshold for dog hemoglobin varies greatly, with an average of about 155 mg per kilogram of body weight. This threshold was depressed by as much as 46 per cent on daily diminishing injections. All types may be paroxysmal in nature, but, generally speaking, it would be well to limit the title of paroxysmal to the nocturnal and cold hemolysin phenomena. Inasmuch as many troops are exposed to low temperatures (Arctic regions and high altitude flying), it is believed that the presentation of the pertinent findings for a patient suffering from the cold type of paroxysmal hemoglobinuria together with a review of some of the literature relative to the subject might be of value.

The first published report of a case of paroxysmal hemoglobinuria was that of a 10 year old child with congenital syphilis presented by Dresler in 1854.<sup>7</sup> In this case, as well as in a similar one published by Elliotson in 1831 and in another by Stewart in 1794,<sup>7</sup> the condition was cured with quinine, so it may have been caused by malaria. In 1866 Parry differentiated plain paroxysmal

4 Jones, C M. Study of Bile Pigments by Means of Duodenal Tube in Paroxysmal Hemoglobinuria, *M Clin North America* 5 1421 (March) 1922

5 Lichty, J A, Jr, Havill, W H, and Whipple, G H. Renal Thresholds for Hemoglobin in Dogs, *J Exper Med* 55 603 (April) 1932. Havill, W H, Lichty, J A, Jr, Taylor, G B, and Whipple, G H. Renal Threshold for Hemoglobin in Dogs Uninfluenced by Mercury Poisoning, *ibid* 55 617 (April) 1932. Havill, W H, Lichty, J A, Jr, and Whipple, G H. Tolerance for Mercury Poisoning Increased by Frequent Hemoglobin Injections, *ibid* 55 627 (April) 1932. Newman, W V, and Whipple, G H. Hemoglobin Injections and Conservation of Pigment by Kidney, Liver and Spleen, *ibid* 55 637 (April) 1932.

6 Gilligan, D R, Altschule, M D, and Katersky, E M. Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, *J Clin Investigation* 20 177 (March) 1941. Lichty and others.<sup>5</sup>

7 Mackenzie, G M. Paroxysmal Hemoglobinuria. A Review, *Medicine* 8 159 (May) 1929

1 Best, C H, and Taylor, N B. The Physiological Basis of Medical Practice, ed 2, Baltimore, William Wood & Company, 1939, p 79

2 Hueper, W C. Reactions in the Blood and Organs of Dogs on Intravenous Injections of a Solution of Hemoglobin, *J Lab & Clin Med* 29 628 (June) 1944

3 (a) Ham, T H. Studies on the Destruction of Red Blood Cells. I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, *Arch Int Med* 64 1271 (Dec) 1939. (b) Ham, T H, and Dingle, J H. Studies on the Destruction of Red Blood Cells. II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum Complement, *J Clin Investigation* 18 657 (Nov) 1939

hemoglobinuria from malarious blackwater fever. The same year Gull showed the relation of chilling to the phenomenon.<sup>7</sup> In 1880 Rosenbach originated the contemporary Rosenbach test, producing hemoglobinuria in susceptible persons by immersing the feet in iced water and then warming them. In 1881 Ehrlich demonstrated, by detecting free hemoglobin in the blood drawn from a finger to which a tourniquet had been applied at its base and then immersed in cold water, that hemoglobin was formed locally in the part chilled, probably due to the production of a lysin by the endothelial cells of the surface blood vessels. He thus agreed with Lichtheim (1876) who proved that hemoglobinuria is a result of excretion by the kidneys of hemoglobin that had been formed in the blood vessels and not, as had been previously believed, produced by the kidney.<sup>7</sup> In 1904 Donath and Landsteiner<sup>8</sup> made thorough serologic investigations of the phenomenon and made clear the following facts: (1) that a lysin is present in the plasma or serum of patients suffering from this disease which can unite with red blood cells only at low temperatures, (2) that the hemolytic action takes place in two phases: (a) the union of the lysin with the red cells at a low temperature and (b) lysis of the red cells on warming, (3) that complement is essential for the second phase of the reaction, (4) that the lysin is an isohemolysin and an autohemolysin, and (5) that the patient's red cells are not hemolyzed by the serum of a normal person of the same grouping (AB, B, A, O). These dictums of Donath and Landsteiner, shown diagrammatically in figure 1, are acceptable today.

Most of the earlier workers realized the association of syphilis, preponderantly of the congenital type, with the disease, there being syphilitic stigmas exhibited in about one third of the cases. Since the discovery of the Wassermann reaction (1906), proof of this association has become overwhelming. In a review by Donath and Landsteiner,<sup>9</sup> there were 95 persons with syphilis in 99 patients reported on. It is apparent that there may be two almost specific tissue reactions in infections with the *Treponema pallidum*, one producing the "reagin" of the Wassermann reaction and the other the "cold hemolysin." In 1925 Nanba<sup>10</sup> produced a cold hemolysin in rabbits by intraperitoneal injections of emulsions of organs (liver, kidney and spleen) of various

animals. It had been shown that similar treatment will produce a positive reaction to the Wassermann test in rabbits. Clinically, however, production of the "cold hemolysin" in syphilis is rare. Whereas it can be said that 95 per cent of the persons with paroxysmal hemoglobinuria due to the cold hemolysin are also syphilitic, only a small portion of persons with syphilis exhibit paroxysmal hemoglobinuria. From the practical view, the decided value of antisiphilitic therapy as a cure of the disease is somewhat convincing evidence of its causation. Certainly it is a good guide for the clinician's approach to the problem. It is to be emphasized that this important place of syphilis applies in only the cases of the disease due to the cold hemolysin and not to any of the other forms mentioned in the opening paragraph.

While the serologic phenomena are qualitatively uniform, the signs and symptoms of the disease may vary considerably. Hemoglobinuria may develop readily in some susceptible persons. Thus Mackenzie<sup>7</sup> reported 1 patient suffering

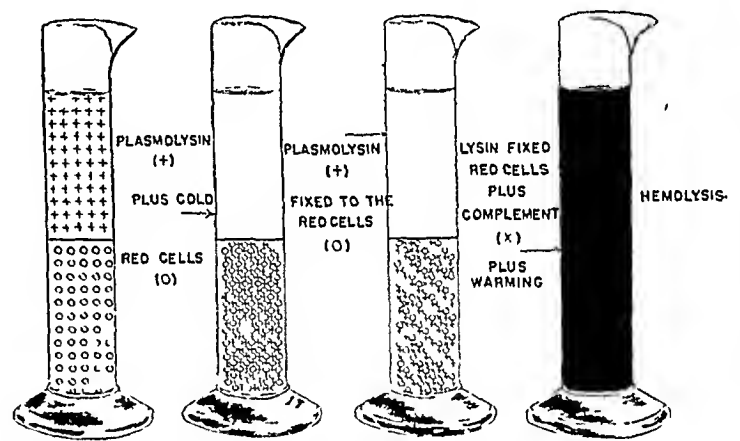


Fig 1—Mechanism of the cold hemolysin. The lysin (+) in the plasma is fixed to the red cells (O) by lowered temperature, the necessary degree of which depends on the individual susceptibility. Complement (X) plus rewarming produces hemolysis of the lysin-fixed cells.

a paroxysm in New York city during July. In other cases, as in the one reported in this paper, rather extreme low temperatures were required. The reaction, both the fixation of the lysin to the erythrocytes on exposure to the cold and the hemolysis of the red cells on warming, probably takes place in the surface vessels of the skin only. The inhalation of extremely cold air or the drinking of ice water will not precipitate an attack even in especially susceptible persons (Boas and Luzzati and Sorgente, cited by Mackenzie), whereas placing the hands or feet in ice water and then warming them, as in the Rosenbach test, may initiate a violent paroxysm. Stevenson<sup>11</sup>

<sup>11</sup> Stevenson, I. P. Paroxysmal Hemoglobinuria with Report of a Case, *McGill M. J.* **12** 192 (Oct) 1943.

<sup>8</sup> Donath, J. and Landsteiner, K. Ueber paroxysmale Hamoglobinurie, *Munchen med. Wchnschr.* **51** 1590, 1904. Mackenzie.<sup>7</sup>

<sup>9</sup> Donath, J., and Landsteiner, K. Ueber Kalte Hamoglobinurie, *Ergebn. d. Hyg., Bakt.* **7** 184, 1925.

<sup>10</sup> Nanba, M. Ueber die kunstliche Erzeugung des Autohamolysins, *Deutsche med. Wchnschr.* **51** 594 (April 10) 1925. cited by Mackenzie.<sup>7</sup>

reported a case in which the ordinary Rosenbach procedure precipitated an almost complete anuria and the patient was critically ill for several days until renal function was gradually restored. Such a reaction could well be due to casts of hematin obstructing the glomerulotubular apparatus. Aside from such extremes are the persons with latent disease in whom, usually persons with syphilis, no signs or symptoms exist but the Donath-Landsteiner reaction of the blood is positive. Also, there are subjects in whom chilling will produce an albuminuria, general malaise, anemia and a leukocytosis but no hemoglobinuria. Thus, even though hemoglobinuria is not demonstrated clinically, in persons with unexplained anemia and transitory albuminuria the disease should be suspected. This is especially true if the patient is known to have syphilis. Less commonly does the individual patient's susceptibility vary, although it has been shown that the thermolability of the isohemolysin may vary from time to time in a given patient. Yorke and Macfie<sup>12</sup> demonstrated that after frequent episodes of hemoglobinuria a patient's serum may be negative to the Donath-Landsteiner test, presumably due to the exhaustion of complement or to the formation of anti-complement. From *in vivo* experiments, it is difficult to conclude whether the variety of responses is due to changes in the complement or the isohemolysin. Also, the influence of the length of time to which the patient is subjected to the cold stimulus may vary. Yorke and Macfie showed that chilling for five to seven minutes resulted in a greater hemolysis than did that for a period of thirty minutes. They suggested that there might be some degradation of the isohemolysin after long exposure to cold or that the longer time allowed a greater distribution of complement midpiece to more erythrocytes. No entirely satisfactory explanation can be given for the symptoms presented by various sufferers, although it is probable that the titer of the isohemolysin determines the severity of the disease. The patient here reported on had no symptoms whatever during his attacks, even when, as in one paroxysm, the red cells fell to 2,510,000 and the hemoglobin content to 52 per cent. In other cases general malaise, chills and weakness have developed. Some patients exhibit pronounced vasomotor changes, such as a Raynaud syndrome, urticaria and vesicle formation in the epidermis. Albuminuria is a constant sign, and leukocytes and casts of pigment bodies are frequently found in the urine. At times the blood pressure falls, and at others

it may become elevated. Often the patient's temperature increases.<sup>7</sup>

The case here reported is that of a 26 year old white man just finishing training as an aerial gunner with a heavy bomber crew. He had always been healthy and, indeed, had no untoward symptoms on presenting himself to the medical officer. He stated that his mother suffered from a mild form of arthritis but had always been well otherwise. The condition of his father, aged 53, and separated from the family, was unknown. One half-brother died from suffocation in infancy. There was no history of familial disease. The patient had spent six weeks in Hawaii with the navy in 1932 but had had no illness during that time. He had been married for six years, and his wife was well except for an indefinite cardiac complaint associated with fainting spells. She had had one pregnancy, which resulted in a spontaneous abortion in the early weeks "due to a fall." On induction into the army and on at least one routine check-up since, the reaction to the Kahn test of the blood had been reported negative. He had been proficient in his training, most of which had been at comparatively low altitudes, although temperatures as low as 21° F (−5° C) had been experienced without difficulty. Two weeks before complaining to his flight surgeon, the patient had noticed, soon after landing from a high altitude flight during which temperatures as low as minus 6° F (−14° C) had been reached, that the voided urine was black. Inasmuch as he felt completely well and as another specimen of urine voided a little later was of normal color, the patient dismissed the incident. He said that he had had moderate difficulty with the oxygen mask frosting on the flight, and he felt that this had been the cause. He had been chilly while at the high altitude, in spite of the sheepskin-lined clothes worn. He made similar flights on ten succeeding nights, and each time he voided one specimen of black urine three or four hours after landing. On one occasion he noted that the urine passed immediately after landing was of normal color but urine voided three hours later was black. On study, the patient appeared rugged and well. The physical examination revealed a soft functional systolic murmur at the base of the heart, normal blood pressure readings and active pupillary, cutaneous and deep tendon reflexes. The reaction of the blood to the Kahn test was negative, but a Wassermann test asked for after this finding was reported as eliciting a positive reaction. The red cell count was 3,580,000, with a hemoglobin content (Sahli) of 78 per cent and a leukocyte count of 6,300, normally distributed differentially. The sedimentation rate was 20 mm in one hour. These values were about the same on three successive examinations within the next four days. The fragility of the red cells to saline solution showed hemolysis beginning at 0.42 per cent and complete at 0.36 per cent (within normal limits). The nonprotein nitrogen content of the blood was 30, and the sugar content was 93 mg per hundred cubic centimeters. The reaction to the Donath-Landsteiner test was positive, there being rather pronounced hemolysis of both the cells of the patient and the cells from a normal person of a similar group (A) by the patient's serum. The serum of the normal control did not hemolyze the red cells of the patient. Results of tests for isoagglutinins were negative. The icteric index was 5. (Of special interest was the demonstration once again of the fact that the isohemolysin is in the susceptible person's serum and that this isohemolysin leaves the serum to become fixed in the red cells when exposed to the cold. Here, a 2 per cent saline suspension of the patient's washed red cells was

<sup>12</sup> Yorke, W., and Macfie, J. W. S. The Mechanism of Autolysis in Paroxysmal Haemoglobinuria, *Brit J Exper Path* 2:115 (June) 1921.

mixed with an equal volume of his serum and refrigerated for ten minutes at 4 C. Immediately after refrigeration the serum was drawn off and was used to perform a complete Donath-Landsteiner test, only the red cells of a normal person being used. No hemolysis took place. The urine was clear and yellow, with a specific gravity of 1.007 and a  $pH$  of 6.5. It contained no glucose but did show a trace of albumin and an occasional leukocyte. It is of interest to note that the acidity of this specimen of urine associated with a trace of albumin and some leukocytes in the sediment because, as will be seen, during a paroxysm induced later the urine became strongly acid, the albumin in-

perature of 21 F (−6 C) for forty-five minutes. During the latter exposure the patient complained of being chilly—"about the same as at high altitude." Blood counts and urinalyses before and after this chilling, demonstrating a paroxysm of hemoglobinuria, are recorded in table 1. Photographs of the urine are shown in figures 2 and 3. After three days the erythrocyte count had returned to 3,640,000, the hemoglobin content to 70 per cent and the leukocyte count to 7,400, with polymorphonuclear cells 59 per cent, lymphocytes 30 per cent, mononuclears 12 per cent, eosinophils 5 per cent and myelocytes 3 per cent. At the end of twenty days the red cells had returned to

TABLE 1—Comparison of Condition of Patient During Refrigeration Experiments

Elapsed Time	Blood			Urine					
	Red Blood Cells	White Blood Cells	Hemoglobin, %	Appearance	Specific Gravity	Albumin	Sugar	Microscopic	$pH$
<i>A</i>									
Before refrigeration	3,710,000	7,800	72	Clear, yellow	1.014	0	0	Negative	6.0
After refrigeration zero	3,680,000	4,950	70	Cloudy, straw	1.012	0	0	Few white cells	6.0
½ hour	3,700,000	5,100	75	Cloudy, straw	0.012	0	0	Few white cells	6.0
1 hour	3,715,000	4,800	72						
1½ hours	3,500,000	5,500	70						
2 hours	3,420,000	6,200	70	Cloudy, straw	0.014	0	0	Few white cells	6.0
2½ hours	3,200,000	7,600	65	Cloudy, straw	1.010	Trace	0	Many white cells	5.5
3 hours	3,000,000	9,400	62	Brown	1.021	1+	0	Many white and red cells and pigment casts	5.5
3½ hours	2,510,000	13,500	52	Very dark	1.022	1+	0	Many white and red cells and pigment casts	5.5
4 hours	2,600,000	11,000	55	Slightly dark	1.020	1+	0	Many white and red cells and pigment casts	5.5
5 hours				Clear, straw	1.010	0	0	Few white cells	7.0
<i>B</i>									
Before refrigeration	3,830,000	6,300	70	Clear, yellow	1.012	0	0	Negative	7.5
After refrigeration zero	3,800,000	5,100	70	Clear, yellow	1.014	0	0	Negative	7.5
½ hour	3,560,000	4,800	65	Clear, yellow	1.012	0	0	Negative	7.5
1 hour	3,750,000	5,100	68	Clear, yellow	1.018	0	0	Negative	7.5
1½ hours	3,780,000	6,400	70	Clear, yellow	1.014	0	0	Negative	7.5
2 hours	4,040,000	7,100	70	Clear, yellow	1.008	0	0	Negative	6.5
2½ hours	4,260,000	8,300	72	Clear, straw	1.006	0	0	Negative	6.5
3 hours	4,180,000	7,600	72	Clear, yellow	1.010	0	0	Negative	7.5
3½ hours	4,010,000	6,600	70	Clear, yellow	1.012	0	0	Negative	7.5
4 hours	4,260,000	5,800	72	Clear, yellow	1.012	0	0	Negative	7.5
5 hours	4,100,000	4,900	70	Clear, yellow	1.010	0	0	Negative	7.5
<i>C</i>									
Before refrigeration	4,520,000	4,800	76	Clear, yellow	1.010	0	0	Negative	6.0
After refrigeration zero	4,600,000	4,500	75	Clear, yellow	1.010	0	0	Negative	6.0
½ hour	4,200,000	6,200	72	Clear, yellow	1.010	0	0	Negative	6.0
1 hour	4,120,000	6,600	70	Cloudy, straw	1.016	0	0	Few white cells	6.0
1½ hours	3,800,000	6,500	68	Cloudy, straw	1.020	0	0	Few white cells	6.0
2 hours	3,810,000	7,800	62						
2½ hours	3,600,000	9,000	60	Cloudy, straw	1.020	2+	0	Many white and red cells	5.5
3 hours	3,400,000	11,000	58	Cloudy, brown	1.022	2+	0	Many white and red cells	6.0
3½ hours	4,000,000	9,200	60	Cloudy, yellow	1.018	Trace	0	Many white cells	7.0
4 hours	4,120,000	8,700	66	Clear, straw	1.010	0	0	Negative	7.0

In A are tabulated the blood and urinary findings during the refrigeration experiment on the patient's admission and without medication, while in B are the findings in the same experiment after rapid and pronounced alkalization of the urine with sodium bicarbonate has given the patient protection. In C the patient is still receiving alkali, but the effectiveness has diminished. The latent period following the chilling and warming is well demonstrated in A and C. See table 2 for Donath-Landsteiner tests corresponding to these experiments.

creased and blood cells and pigment casts appeared (table 1). On the succeeding days the urine was entirely normal and albumin free, and the  $pH$  varied from 6.5 to 7.5. At first, the patient was observed after he had sat on the open porch for thirty minutes with the temperature at 32 F (0 C). Even though clothed in light summer underwear and trousers and a light woolen shirt, he did not become uncomfortable during the period nor did hemoglobinuria develop. He was then placed in a large storage refrigerator for one hour at 28 F (−2 C), and again he had no untoward symptoms. A few days later he was exposed to the same temperature for one hour, followed by a tem-

perature of 21 F (−6 C) for forty-five minutes. During the latter exposure the patient complained of being chilly—"about the same as at high altitude." Blood counts and urinalyses before and after this chilling, demonstrating a paroxysm of hemoglobinuria, are recorded in table 1. Photographs of the urine are shown in figures 2 and 3. After three days the erythrocyte count had returned to 3,640,000, the hemoglobin content to 70 per cent and the leukocyte count to 7,400, with polymorphonuclear cells 59 per cent, lymphocytes 30 per cent, mononuclears 12 per cent, eosinophils 5 per cent and myelocytes 3 per cent. At the end of twenty days the red cells had returned to

4,360,000, with 70 per cent hemoglobin. The sharp increase in the acidity of the urine to a  $pH$  of 5.5 was striking and worthy of discussion. In his studies of the destruction of the red blood cells in cases of paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli type), Ham<sup>3a</sup> surmised that the hemoglobinuria might be due to a decrease of the  $pH$  of the blood, it having been demonstrated that the carbon dioxide content of the blood was increased during the hypoventilation of the lungs during sleep.

To combat this "acidity," Ham administered 65 Gm of sodium bicarbonate during the twenty-four hours prior to testing and found a pronounced reduction of hemoglobinuria in 2 cases. It has also been observed that thorough alkalization of the urine is of benefit in combating the hemoglobinuria of blackwater fever.<sup>13</sup> There are no reasons to believe that the carbon dioxide content of the blood in the patient here reported was increased either during his flights at high altitude, when oxygen was used continuously above 10,000 feet (3,000 meters), or during the refrigeration

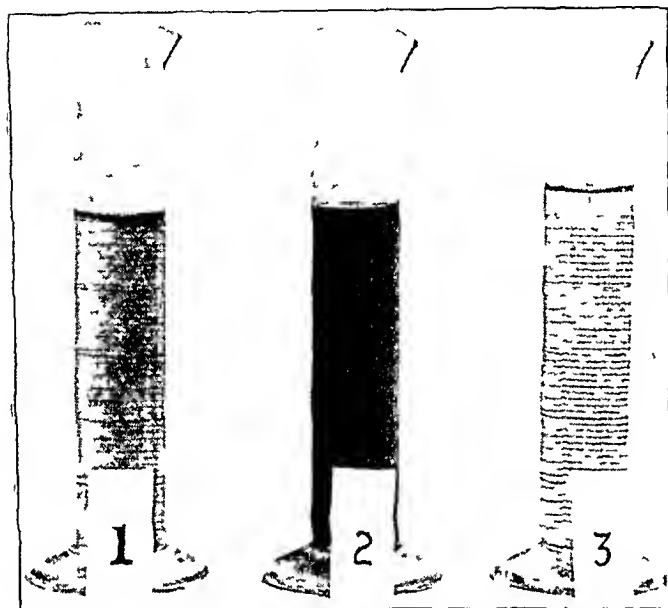


Fig 2—The graduate marked 1 is a photograph of the patient's urine prior to exposure to the cold, graduate 2 illustrates the intensity of the hemoglobinuria occurring three hours after the exposure was stopped, and graduate 3 demonstrates the clear urine another two hours later

experiments. Nevertheless, the urine became intensely acid. It was this observation that prompted the decision to "alkalize" the patient and to repeat the experiment as shown in *B* of table 1. It is seen that after the administration of 32 Gm of sodium bicarbonate in twenty hours the urine reached a  $p_H$  of 7.5, the Donath-Landsteiner test was less positive and that hemoglobinuria with the associated blood changes did not develop during the exact reduplication of the refrigeration and warming. However, a repetition of the same experiment after the patient had been given 12 Gm of the alkali daily for a period

13 (a) Baker, S. L., and Dodds, E. C. Obstruction of Renal Tubules During Excretion of Hemoglobin, *Brit J Exper Path* 6:247 (Oct) 1925. (b) Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, ed 6, Philadelphia, The Blakiston Company, 1942, vol 1, p 160. (c) Circular Letter no 56, United States War Department, Office of the Surgeon General, Washington, D. C., Government Printing Office, 1942.

of thirty days demonstrated a relapse in spite of an alkaline urine. During this period several tests revealed a positive Donath-Landsteiner reaction. In *C* of table 1 are recorded the phenomena of the "cold" hemolysin once more at work. In table 2 are shown the results of the Donath-Landsteiner tests done with each experiment *A*, *B* and *C* of table 1. In *D* of table 2 is shown an isolated test done on rapid, intensive alkalization of the urine with sodium bicarbonate for the first time. As the results of this test were entirely negative it would appear that the drug was most efficacious when first administered, losing its effectiveness by degrees as time went on.

Several authors have studied the mechanism of hemoglobinuria and the effects of hydrogen ion concentration on it.<sup>14</sup> It is probable that a vasodilatation of the capillaries<sup>14a</sup> allows the large hemoglobin molecule (molecular weight 68,000) to pass through the renal glomerulus and into the tubule, where some reabsorption takes place. The process of reabsorption may depend on one

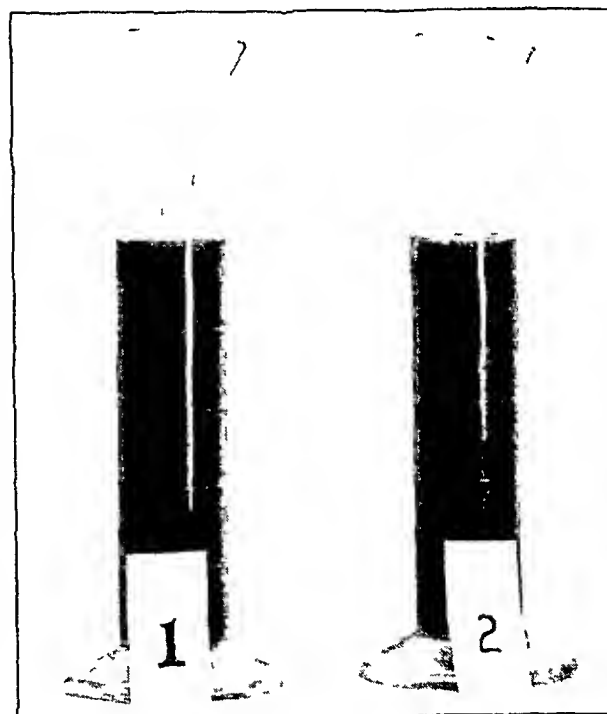


Fig 3—The graduate marked 1 illustrates the hemoglobinuria two hours after flight, while graduate 2 shows the urine three hours following exposure to the cold in the refrigeration experiment. The hemoglobinuria following the patient's flight is more intense.

or both of two factors: (a) the electrical charge carried by the protein molecule itself and (b) the charge carried by the tubule membrane, the electrical charge associated with the various

14 Yule, C. L. Hemoglobinuria, *Physiol Rev* 22:19 (Jan) 1942.

14a Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1929.

hydrogen ion concentrations effecting changes in the permeability, alkalinity favoring and acidity tending to prevent reabsorption<sup>15</sup> Webster and colleagues<sup>16</sup> demonstrated, in experiments on frog kidney perfused with hemoglobin solutions of various  $p_H$ , that acidity increased and alkalinity decreased the elimination of hemoglobin. They suggested that the more acid solutions increased the permeability of the glomerular capillaries, letting more molecules of hemoglobin through, or that the lower  $p_H$  values changed the dissociation state of the molecule, allowing it to pass the negatively charged glomerular membranes more easily. Walbum<sup>17</sup> showed the effects of hydrogen ion concentrations on the hemolyzing properties of various bacteriolysins (*Bacillus welchii*, *Clostridium septicum*, *Bacillus oedematiens* and *Bacillus tetani*), using in vitro experiments on horse

TABLE 2—Results of Donath-Landsteiner Tests

Serum of Patient, Cc	Cells of Patient, Cc	Hemolysis	Serum of Patient, Cc	Cells of Patient, Cc	Hemolysis
A			D		
0.10	0.50	Trace	0.10	0.50	0
0.20	0.50	1+	0.20	0.50	0
0.30	0.50	1+	0.30	0.50	0
0.50	0.50	2+	0.50	0.50	0
B			E		
0.10	0.50	0	0.10	0.50	Trace
0.20	0.50	0	0.20	0.50	1+
0.30	0.50	Trace	0.30	0.50	1+
0.50	0.50	1+	0.50	0.50	2+
C			F		
0.10	0.50	Trace	0.10	0.50	0
0.20	0.50	1+	0.20	0.50	0
0.30	0.50	1+	0.30	0.50	0
0.50	0.50	2+	0.50	0.50	0

A shows the results of the Donath-Landsteiner test, increasing amounts of the patient's serum being used with a standard amount of a 5 per cent suspension of the patient's washed erythrocytes during the experiment of A in table 1. B and C are the tests for experiments B and C in table 1. D was done soon after sodium bicarbonate in large doses was given for the first time when the urine reached an alkalinity of over  $p_H$  7.5. It was the only time prior to completion of antisyphilitic therapy that the Donath-Landsteiner test was entirely negative. E shows the test after half the oxophenarsine hydrochloride and bismuth subsalicylate treatments had been received and F the result at the end of the entire course of therapy.

blood corpuscles. He demonstrated an optimum and a minimum point for hemolysis, below and above which  $p_H$  the degree of hemolysis would be increased or decreased respectively. The hemolytic action varied for each bacteriolysin. His work deserves greater investigation, with possibilities of valuable clinical application in therapy. Baker and Dodds<sup>18</sup> showed that when the con-

centration of sodium chloride is 1 per cent urine with a  $p_H$  of below 6.0 will precipitate hemoglobin in the kidney tubule, possibly causing obstruction. They showed that in vitro hemoglobin is thrown out of solution when the  $p_H$  of the medium is not more than 6.0 and the sodium chloride content 1 per cent or more. They suggest alkalization of the urine in all forms of hemoglobinuria—blackwater fever, transfusion reactions and paroxysmal hemoglobinuria. De Navasquez<sup>19</sup> disagreed with the theory of precipitation of hemoglobin in the tubules when the urine is more acid. He reported 2 cases of death following transfusion reactions in which no such intratubular precipitation occurred in spite of an acid urine. He stated that hemoglobin is excreted in both alkaline and acid urines provided the volume flow through the glomerulus is sufficient, in fact, he demonstrated a better elimination of hemoglobin and its products with acid urine when the volume flow was the same. In the case here presented it is suggested (in D of table 2) that the  $p_H$  of the kidney urine takes no part, or at least its place is secondary, in paroxysmal hemoglobinuria. It would seem that alkalization definitely prevents the production of a hemoglobinemia somewhere in the lysin fixation-hemolysis mechanism. Its action is somewhere in the peripheral blood or blood vessels. W. Jacobi (cited by Krogh,<sup>14a</sup> page 178) demonstrated that alkaline solutions placed topically on the web of a frog enhanced the vasoconstrictor action of epinephrine. Although he ascribed this phenomenon to a better absorption of the epinephrine through the frog's epidermis, such could not be the entire case, for with the alkalinity the weak epinephrine solutions constricted vessels on which they ordinarily would have had no effect even when placed directly on them. Could it be that the increased alkalinity in the case of our patient initiated vasoconstriction synergistically with the epinephrine of the blood so that either the endothelial cells could not produce the hemolysin or that the constricted capillaries of the glomeruli would not allow the hemoglobin molecule to pass through with the filtrate? Inasmuch as the absence of hemoglobinuria after the use of sodium bicarbonate, as demonstrated in B of table 1, would indicate that increased alkalinity had subdued the influence or the manufacture of the lysin, it is probable that, should an increase in the action of epinephrine be the responsible factor, the efficaciousness of the sodium bicarbonate lies in its synergistic action with epinephrine on the vasoconstrictor apparatus so that the lysin is not

<sup>15</sup> Risse, O, cited by Webster and others<sup>16</sup>

<sup>16</sup> Webster, M. D., Engel, F. L., Laug, E. P., and Amberson, W. R. Influence of  $p_H$  upon the Elimination of Hemoglobin by a Perfused Frog's Kidney, *J. Cell & Comp. Physiol.* 5:399 (Dec. 20) 1934.

<sup>17</sup> Walbum, L. E. Importance of Hydrogen Ion Concentration in Haemolysis by Lysins of Anaerobic Bacteria, *J. Path. & Bact.* 46:85 (Jan.) 1938.

<sup>18</sup> De Navasquez, S. Excretion of Haemoglobin, with Special Reference to "Transfusion" Kidney, *J. Path. & Bact.* 51:413 (Nov.) 1940.

produced on that the lysin fixation-hemolysis mechanism is interrupted in the peripheral vessels. In *A* and *C* of table 1, it is clearly demonstrated that erythrocytes, leukocytes and albumin appear in the urine before the hemoglobinuria develops. This would seem to indicate strongly that some lesion is created in the glomerulo-tubular apparatus, probably by the cold lysin, allowing the excretion of hemoglobin rather than that the hemoglobin caused the renal lesion.

As has been stated, it was Ham's experience<sup>31</sup> with paroxysmal nocturnal hemoglobinuria that the improvement effected by alkalization of the urine was temporary, there being a recurrence of the hemoglobinuria in spite of continued use of sodium bicarbonate. He also discovered that there was a sharp rise in the hemoglobinuria in his 2 patients soon after the discontinuance of the drug. It is remarkable that the effect of alkalinity should be of some efficaciousness in either case, and it is especially remarkable that the two types of hemoglobinuria should be similarly affected. In Ham's work with the Marchiafava-Micheli type, the lysin is inherent with the erythrocytes, while with the case of the "cold" hemolysin the lysin is the property of the serum—yet the two types are affected alike by the use of sodium bicarbonate. Although it would seem that alkalinity was the important factor in the changes brought about by the sodium bicarbonate, this statement cannot be made definitely, as the responsible agent may have been the sodium ion. However, Baker and Dodds<sup>13a</sup> showed that hemoglobinuria was easily produced in their experiments when the urine was acidified by the use of sodium sulfate, thus placing the onus on the basic radical. Although this patient had been taking 12 Gm of sodium bicarbonate daily for thirty days, so that the urine was held at a  $p_H$  of 7.5, hemolytic phenomena occurred on the usual refrigeration, and the Donath-Landsteiner reaction was consistently positive (table 1 *C*) in spite of the administration of an additional 20 Gm forty-eight hours prior to the test. The patient continued his high altitude flying at low temperatures in the interim but had been provided with electrically heated clothing. He had noted no dark-colored urine during this regimen. As soon as it was demonstrated that the use of sodium bicarbonate was of no lasting value and as serotherapy, once thought to be of help,<sup>19</sup> had been proved useless,<sup>20</sup> antisyphilitic therapy was begun

with a course of forty 0.06 Gm doses of oxophenarsine hydrochloride given intravenously and sixteen 0.20 Gm intramuscular injections of bismuth subsalicylate. As it was felt that any improvement in the patient's hemoglobinuria might be used as a quantitative test in the judgment of the efficacy of this rather short course of therapy, a Donath-Landsteiner test was performed when half the treatment had been finished and at the end of the entire course. *E* and *F* of table 2 show the result of the test at each of these stages of therapy. It is seen that at the half-way point there was no improvement in the test for the lysin, whereas apparent cure as indicated by the negative Donath-Landsteiner test was effected at the end of the treatment. Probably this can be used as another criterion for the efficacy of the short, intensive course of syphilotherapy currently used in the army. No clinical signs of syphilis appeared at any time in this patient, and at the end of his course of therapy the reaction to the Kahn test of the blood was negative and the Wassermann reaction anti-complementary. The results of examination of the spinal fluid, done when he was first seen, were negative.

#### SUMMARY

A case of paroxysmal hemoglobinuria in an aerial gunner with probable syphilis who was subject to attacks when exposed to the low temperatures of high altitudes is presented. The temperatures to which he was subjected in flying were duplicated in experiments in which the patient was placed in a storage refrigerator, and hemoglobinuria with its attendant signs of blood destruction was observed. Some transient benefit was noted with alkalization of the urine with sodium bicarbonate. The currently prescribed course of forty 0.06 Gm doses of oxophenarsine hydrochloride administered intravenously and sixteen 0.20 Gm doses of bismuth subsalicylate given intramuscularly cured this disease, as evidenced by the development of a negative reaction to a Donath-Landsteiner test. In cases of unexplained anemia, especially but not necessarily in a patient known to be exposed to low temperatures, the phenomenon of paroxysmal hemoglobinuria due to the "cold" hemolysin should be suspected. The search for syphilis by history and by physical examination and serologically (the Wassermann reaction being used in the cases in which the Kahn reaction was negative) is important both as an aid to diagnosis and as an indication for treatment. Some theoretic considerations of the phenomenon of paroxysmal hemoglobinuria are presented.

<sup>19</sup> Widal and Rostaine. Sérothérapie préventive de l'attaque d'hémoglobinurie paroxystique, *Compt rend Soc de biol* 58 397, 1905.

<sup>20</sup> Montagnani, M. Crise hémoclasique et hémoglobinurie paroxystique, *Presse med* 29 1017 (Dec 24) 1921, cited by Mackenzie.

# CONGENITAL IDIOPATHIC METHEMOGLOBINEMIA

## FAVORABLE RESPONSE TO ASCORBIC ACID THERAPY

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The purpose of this report is to describe the observations in a case of congenital idiopathic methemoglobinemia and the favorable response of the patient to ascorbic acid therapy. Methemoglobinemia of a congenital and spontaneous origin is an unusual condition, infrequently reported in the literature. The occurrence of cyanosis because of a high blood level of methemoglobin in two or more members of the same family is referred to as familial idiopathic methemoglobinemia. Among the cases of this type appearing in the literature, the cyanosis has usually been present since the patient's birth but in a few instances has not been observed until later in childhood. This should not be confused with methemoglobinemia of enterogenic origin, such as is described by Stokvis,<sup>1</sup> Talma,<sup>2</sup> van den Bergh,<sup>3</sup> Gibson and Douglas,<sup>4</sup> Lichtenbelt<sup>5</sup> and Wynter,<sup>6</sup> in which the elevated methemoglobin concentration is associated with autointoxication produced by chronic persistent diarrhea or obstipation and which usually disappears when these conditions are brought under control.

Pertinent data on idiopathic methemoglobinemia as reported in the literature are presented in table 1. The first report of congenital cyanosis of long duration in which congenital heart disease and pulmonary disorder were ruled

out was that of François,<sup>7</sup> in Belgium, in 1844. It was not until 1912, however, that Slosse and Wybauw,<sup>8</sup> also of Belgium, described idiopathic cyanosis in which the presence of methemoglobin was confirmed by spectroscopic examination. Although their patient had a systolic pulmonic murmur, the cyanosis was thought to be associated with the methemoglobin found in the blood, which disappeared in vitro when a reducing agent was added. This patient, unlike those whose disease is of enterogenic origin, did not have any intestinal trouble, nor did changes in the dietary regimen or purges affect the cyanosis.

The case reports compiled in table 1, with 1 exception, concern patients who were free of gastrointestinal complaints—that is, free from persistent diarrhea or constipation. The 1 exception is the case described by Miller,<sup>9</sup> in which the young girl had obstinate constipation and excessive indicanuria. The daily use of enemas of potassium permanganate solution lessened the degree of cyanosis but failed to efface it completely. The report is included here because the cyanosis dated from birth. Another case in which the mechanism for methemoglobin formation may be different than the others included here is that of Schwartz and Rector.<sup>10</sup> The blood from their patient contained 57 per cent methemoglobin, but no etiologic factors could be ascertained. The baby was given an intravenous injection of a 1 per cent solution of methylthionine chloride. The cyanosis van-

From the Industrial Hygiene Research Laboratory, National Institute of Health

1 Stokvis, B J. Zur Casuistik der autotoxischen enterogenen Cyanosen, Internat Beitr z inn Med **1** 597-610, 1902

2 Talma, S. Intraglobulaire methaemoglobinaemie bij den mensch, Nederl tijdschr v geneesk **38** 721-732, 1902

3 van den Bergh, A A H. Enterogene Cyanose, Deutsches Arch f klin Med **83** 86-106, 1905

4 Gibson, G A, and Douglas, C C. Microbic Cyanosis, Lancet **2** 72-74 (July 14) 1906

5 Lichtenbelt, J W T. Intraglobulaire Methaemoglobinaemie, Geneesk gids **1** 545-552, 1923-1924

6 Wynter, W E. Methaemoglobinaemia of Twelve Years Standing, Proc Roy Soc Med (Clin Sect) **1** 48, 1907-1908

7 François. Cas de cyanose congenitale sans cause apparente, Bull Acad roy de med Belgique **4** 698-700, 1844-1845

8 Slosse, A, and Wybauw, R. Un cas de methemoglobinemie idiopathique, Ann et bull Soc roy d sc med et nat de Bruxelles **70** 206-214, 1912

9 Miller, R. A Case of Enterogenous Methaemoglobinemia (? Congenital) in a Child, Arch Dis Childhood **5** 73-75 (Feb) 1930

10 Schwartz, A S, and Rector, E J. Methemoglobinemia of Unknown Origin in a Two Week Old Infant, Am J Dis Child **60** 652-659 (Sept) 1940

ished within thirty minutes and had not returned at the last period of observation, eight months later. The failure of cyanosis to reappear after a single dose of methylthionine chloride, which is lost fairly rapidly by excretion, places this case in a group separate from those just described.

The case reported by Dieckmann<sup>11</sup> is unusually interesting. When first observed, the patient was pregnant for the third time, having had one stillborn child and one who died three months after birth. It was stated that during her pregnancies the cyanosis was more intense.

An analysis of these reports reveal (table 1) that 18 cases of idiopathic methemoglobinemia have been recorded to date in the literature. In 8 of these cases the disorder was thought to be of congenital origin only, 6 had both a congenital and a familial history, 2 had a familial history, and in 2 the disease could not be defined as congenital or familial. Only persons of the white race have been described with this disorder. The median age was 29 years, with the entire age range represented. Seven were female, and 11 were males. Nearly all of the cases have been reported since 1930. The en-

TABLE 1—*Tabulation of Pertinent Data from Reported Cases of Idiopathic Methemoglobinemia*

Nationality	Age, Yr	Sex	Duration of Cyanosis, Years	Familial History of Cyanosis	Method of Determining Methemoglobin	Amount of Methemoglobin		Date of Report	Authors
						Gm per 100 Cc	Per Cent of Total Hb		
Belgian	20-22	M	20-22	None		—	—	1844	François <sup>7</sup>
Belgian	37	F	4	None	Spectroscopic	—	—	1912	Slosse and Wybauw <sup>8</sup>
Turkish	26	M	7	None	Gasometric and spectroscopic	—	26	1930	Litarczek and others Sang <sup>4</sup>
British	9	F	9	None	Spectroscopic	—	?	1930	Miller <sup>9</sup>
American	27	F	27	None	Gasometric and spectroscopic	?	?	1932	Dieckmann <sup>11</sup>
German	32	M	32	2 brothers had cyanosis since birth	Gasometric and spectroscopic	—	40	1932	Hitzenberger, K. Wien Arch f inn Med <b>23</b> : 85-96, 1932
Dutch	33	F	33	None	Spectroscopic	—	—	1933	van Thienen, G. J. Nederl tijd schr v geneesk <b>77</b> : 1086-1092 (March 11) 1933
Dutch	16	M	16	None	?	?	?	1933	van Lier, H. W. Thesis, Utrecht, 1933, cited by van Thienen
German	68	M	68	None	Spectroscopic	—	17	1935	Leiner, G. and Minibek, H. Wien klin Wchnschr <b>48</b> : 1547 (Dec 13) 1935
Dutch	37	M	37	Brother and sister had cyanosis	Spectroscopic	—	—	1937	van Heukelom, S. Geneesk tijd schr v Nederl—Indie <b>77</b> : 3054 (Nov 30) 1937
Canadian	37	M	25-26	Sister (next case)	Gasometric and spectroscopic	1.4	11.5	1938	Bensley, Rhea and Mills. Quart J Med <b>7</b> : 325-330 (April) 1938
Canadian	43	F	32	Brother (above case)	Gasometric and spectroscopic	0.7	5.0	1938	Same as case just above
French	36	M	36	Brother (next case) also 1 brother and 2 sisters	Spectroscopic	—	45	1939	Lian, Frumusan and Sassier <sup>12</sup>
French	28	M	28	See above case	Spectroscopic	—	35-40	1939	Same as case just above
American	2 wk	F	2 wk	None	Gasometric and spectroscopic	7.4	57	1940	Schwartz and Rector <sup>10</sup>
British	29	M	29	Brother (next case)	Gasometric and spectroscopic	—	ca 40	1943	Deeny, Murdock and Rogan <sup>13</sup>
British	19	M	19	Brother (above case)	Gasometric and spectroscopic	—	ca 40	1943	Same as case just above
British	?	F	Since birth	None	Spectroscopic	6.2	35	1944	King, Gilchrist and White <sup>14</sup>

When she went into labor for her third term, she had only 7 Gm of functioning hemoglobin per hundred cubic centimeters of blood. A transfusion of 600 cc of whole blood was given, and immediately afterward her skin turned an almost normal color. A normal-appearing baby was delivered without further complications. The cyanotic color did not return during the remaining fourteen days of hospitalization. However, a month after her discharge from the hospital, the cyanosis had reappeared, and a large amount of methemoglobin was found in her blood.

<sup>11</sup> Dieckmann, W. J. Methemoglobinemia, Arch Int Med **50**: 574-578 (Oct) 1932.

tire group may be classified as idiopathic to distinguish these cases from those of methemoglobinemia of enterogenic origin and of other known causes, such as exposure to aniline sulfate or sulfanilamide therapy.

In the majority of the cases just listed, the cyanosis had been attributed to a cardiac defect, usually congenital. Frequently a cardiac murmur was present, and, in some instances, enlargement of the heart was noted. Dyspnea on exertion and tachycardia were frequent findings. There were also complaints of nervousness, irritability, persistent headaches and shortness of breath. Often the skin was described as having a bluish gray color and no underlying reddish tint. The bluish discoloration is par-

ticularly intense about the lips, ears, nose, cheeks, finger nails and mucous membranes of the mouth. Clubbing of the fingers, which is often associated with certain cardiorespiratory disorders, was not reported. In the cases in which the methemoglobin content was measured the concentration varied from approximately 10 to 57 per cent of the total hemoglobin, the median being between 30 and 40 per cent.

Little has been offered in the literature in regard to the mechanism involved in idiopathic methemoglobinemia. A very important observation was made by Dieckmann<sup>11</sup> when he noted that the methemoglobinemia of his patient remained at a constant level. Ordinarily, methemoglobin will gradually disappear if the blood is allowed to stand in a test tube for twenty-four hours at room temperature. Since the blood cells of his patient were found to have normal glycolytic activity, Dieckmann reasoned that "the constancy of methemoglobinemia, then, is probably due to the continued presence or production of a substance capable of oxidizing hemoglobin." Lian, Frumusan and Sassier<sup>12</sup> discovered that the methemoglobin concentration of the blood of their 2 patients had not changed after the blood had stood in a test tube for twenty-four hours and also that the addition of the patients' plasma to normal red cells did not produce any methemoglobin. These workers suggested that the methemoglobinemia was caused by an abnormal resistance to reduction. They also observed the therapeutic benefits of ascorbic acid administration and demonstrated the demethemoglobinizing property of ascorbic acid with in vitro experiments. One of their patients was given a daily intravenous dose of 100 mg of ascorbic acid for three weeks, which resulted in a noticeable diminution of cyanosis and methemoglobin concentration, a disappearance of dyspnea and headache and an increased sense of well-being. The ascorbic acid therapy was then discontinued for ten days, during which time the cyanosis again became conspicuous and the methemoglobin concentration rose to 35 per cent.

Unaware of the work of Lian and his group, Deeny, Murdock and Rogan<sup>13</sup> tried oral administration of ascorbic acid. Their first patient, receiving 150 mg of ascorbic acid twice daily, acquired a normal coloring of the skin in twelve

days of treatment. With the same dosage of ascorbic acid continuing to be given, a month later the oxygen-combining capacity of his blood was found to be 22 volumes per cent in comparison to 13.2 volumes (approximately 35 per cent methemoglobin) before treatment. On the sixty-third day of treatment, the patient's blood contained 11 per cent methemoglobin and 1.55 mg per hundred cubic centimeters of ascorbic acid. The second patient treated by these authors received 200 mg of ascorbic acid daily for two weeks and then 400 mg daily thereafter. During the first month of treatment, the methemoglobin concentration of the blood fell from 43 per cent to 6 per cent, at which level it remained. An initial ascorbic acid level of 0.19 mg per hundred cubic centimeters became stabilized after three weeks of treatment at 1.73 mg. The patient's cyanosis disappeared and strenuous exercise was less exhausting.

A fourth person with idiopathic methemoglobinemia, successfully treated with ascorbic acid, is presented in the report of King, Gilchrist and White<sup>14</sup>. Before treatment, their patient had a blood methemoglobin concentration of approximately 35 per cent and a plasma ascorbic acid level of 0.33 mg per hundred cubic centimeters. After he had received 300 mg ascorbic acid per day for one month, the methemoglobin had dropped to 9 per cent, and the plasma ascorbic acid had risen to 1.37 mg per hundred cubic centimeters. During the second month the daily dose of ascorbic acid was doubled. This did not materially alter the methemoglobin level and raised the ascorbic acid content of the blood only slightly. Approximately one month after the ascorbic acid therapy was discontinued, the methemoglobin concentration rose again to 31.6 per cent, and the plasma level of ascorbic acid returned to the pretreatment level. Gibson<sup>15</sup> was of the opinion that the use of ascorbic acid in the treatment of methemoglobinemia appeared to be limited to those cases in which the normal enzyme systems responsible for reducing methemoglobin were absent or suppressed.

#### REPORT OF A CASE.

During a recent investigation in an ordnance plant, a young woman (B. A.) with pronounced cyanosis, who was working in a nontoxic area, was brought to our attention. She had a dull, gray-purple appearance which was even more conspicuous at short distances (100 ft [33 meters]) than at close view. B. A. was 19

14 King, E. J., Gilchrist, M., and White, J. C. A Case of Methemoglobinemia, *Biochem J* **38** viii, 1944.

15 Gibson, Q. H. The Reduction of Methaemoglobin by Ascorbic Acid, *Biochem J* **37** 615-618, 1943.

12 Lian, C., Frumusan, P., and Sassier. Methemoglobinémie congénitale et familiale. Action favorable de l'acide ascorbique, *Bull et mem Soc med d hôp de Paris* **55** 1194-1203 (July 17) 1939.

13 Deeny, J., Murdock, E. T., and Rogan, J. J. Familial Idiopathic Methaemoglobinaemia with a Note on the Treatment of Two Cases with Ascorbic Acid. *Brit M J* **1** 721-723 (June 12) 1943.

years old and said she had been cyanotic all of her life. None of her living relatives had cyanosis or other related symptoms. Her father, who had died of a heart attack, was said to have been nervous and had suffered from headaches also. Her color, as well as accompanying symptoms of headaches, extreme fatigue and dyspnea with exercise, had been ascribed to a congenital cardiac lesion by a number of physicians. On physical examination, no evidence of a defective heart could be found, nor could the cyanosis be ascribed to chemical or medicinal exposure or to gastrointestinal disorder. Two samples of dark, chocolate-colored blood were taken about two weeks apart and each found to contain approximately 50 per cent methemoglobin. These levels did not change when the samples remained in a test tube overnight. As congenital methemoglobinemia was suspected, the patient was hospitalized for twenty-four days for investigative purposes six months later.

B. A. had always been in fairly good health except for almost continuous severe headaches, dizziness, dyspnea and palpitation on exertion and frequent sore throats. The headaches occurred in the frontal and occipital areas, were throbbing in character and varied in intensity. The patient stated that they usually developed fifteen to twenty minutes after she arose in the morning and continued with increasing intensity throughout the day. She did not suffer from ocular fatigue or blurred vision. She usually took 4 to 6 acetylsalicylic acid tablets a day but would sometimes total as many as 12. Her headaches were severer when her skin was bluer, and both the headaches and the cyanosis were thought to increase before menstruation. Although the dizziness seemed to be worse after menstruation, she generally felt her best at that time. Sixteen months before observation she had given birth to a normal and healthy-appearing female infant. She believed she was less cyanotic and more energetic during the latter part of her pregnancy than she had ever been.

The patient complained that after moderate exercise her heart beat rapidly and heavily and it was difficult for her to breathe. She said that she could walk only one or two blocks if she moved rapidly but a mile (1.6 kilometers) or more if walking slowly and that she was not able to run at all. Her hands and feet tended to be cold and dry, and her feet swelled occasionally. When she attempted to carry packages or the baby, her arms and hands often became cramped. At the time of observation, she stated she had lost strength during the last three or four years. She admitted that she was an irritable person and became upset easily, frequently quarreling with her family and worrying about finances.

Questioning revealed that the patient's dietary regimen was poor, particularly in protein and vitamins. She usually had a sandwich and a Coca Cola for lunch, about six Coca Colas during the day and a regular evening meal. She took no vitamin capsules and rarely ate raw fruits or vegetables, her appetite had always been good.

B. A. was a short, well developed, slightly obese woman of the stated age. Although there was general cyanosis of her skin, it was particularly noticeable over the nail beds, palms, lower half of both legs, lips and oral mucous membranes. Ophthalmoscopic examination demonstrated extremely dark-colored retinal vessels. There was no clubbing of the fingers.

She had a resting regular pulse rate of 80 per minute, which became decidedly accelerated with mild exercise. The heart sounds were of good quality

except for a definite roughness of the pulmonary first sound and an accentuation of the pulmonary second. The average of several readings of blood pressure taken on both arms was 98 systolic and 70 diastolic (millimeters of mercury). The surface area measurement of the heart shadow on a posteroanterior roentgenogram of the chest taken at 72 inches (183 cm) was of normal size as based on the patient's height and weight. The lungs appeared normal on physical and roentgenographic examination. The neurologic examination showed nothing abnormal except hyperactive tendon reflexes.

Electrocardiograms were taken before and after exercise according to the Master exercise test,<sup>16</sup> but the patient was unable to complete the test because of extreme dyspnea. The tracing taken after exercise showed a slight depression of the ST segment in one of the leads, otherwise the tracing appeared normal.

Hemoglobin and methemoglobin were measured by the spectrophotometric method of Horecker and Brackett.<sup>17</sup> On the day of the patient's admission to the hospital, the methemoglobin content was 3.9 Gm per hundred cubic centimeters of blood, or about 25.2 per cent of the total hemoglobin. This value was considerably lower than it had been six months earlier. These differences may have been associated with the patient's menstrual cycle, as the first day in the hospital was the fifth and last day of her menstrual period. The results of the laboratory procedures that were performed repeatedly are presented in table 2. Other laboratory observations included the prothrombin time, red cell size and distribution as measured by the Price-Jones technic, plasma fibrinogen content, glycolytic activity of whole blood and twenty-four hour urinary excretion of coproporphyrin, all of which were within normal limits.

Before vitamin therapy was initiated, ascorbic acid was added to the patient's blood in vitro and was found to reduce the methemoglobin. Then the patient was given 100 mg of ascorbic acid orally, four times daily. During the first seven days of treatment the methemoglobin level gradually dropped from 4.4 Gm to 2.1 Gm per hundred cubic centimeters, the methemoglobin falling from 25 to 11 per cent. The ascorbic acid level of the blood rose from 0.5 to 1.5 mg per hundred cubic centimeters and the urinary level of ascorbic acid from 87 to 1870 mg per twenty-four hour period, as analyzed by the method of Farmer and Abt.<sup>18</sup> The patient seemed more alert and energetic and stated that her headaches were less intense. The cyanosis was diminished but still conspicuous.

Until this time, use of methylthionine chloride had been avoided because of its two contradictory actions on hemoglobin, that is, low concentrations are known to convert methemoglobin to hemoglobin in vivo, but high concentrations produce methemoglobin by converting the ferrous ion to the ferric. These opposing actions have been explained by the reversible oxidation-

16 Master, A. M., Friedman, R., and Dack, S. The Electrocardiogram After Standard Exercise as a Functional Test of the Heart, *Am Heart J* **24** 777-793 (Dec) 1942.

17 Horecker, B. L., and Brackett, F. S. A Rapid Spectrophotometric Method for the Determination of Methemoglobin and Carboxyhemoglobin in Blood, *J Biol Chem* **152** 699-677 (March) 1944.

18 Farmer, C. J., and Abt, A. F. Determination of Reduced Ascorbic Acid in Small Amounts of Blood, *Proc Soc Exper Biol & Med* **34** 146-150 (March) 1936.

reduction system of methylthionine chloride and its leukoform<sup>19</sup> On the eighth day of ascorbic acid therapy, 7 cc of 1 per cent solution of methylthionine chloride was given intravenously Within thirty minutes, the remainder of the patient's cyanosis disappeared A sample of blood taken two hours later contained 0.2 Gm methemoglobin per hundred cubic centimeters The patient claimed that her headache had vanished and that she had a sense of well-being For the first time in her life her skin had a pink color Her hands and feet were warmer, and she was conscious of her palms becoming damp She was able to walk rapidly without tiring or becoming breathless The Master exercise test was repeated, and this time it was completed with ease The depression of the ST segment following exercise which was found in the electrocardiograms taken before treatment was absent A comparison of T waves in leads I and II taken at rest, before and after ascorbic acid therapy revealed a slight increase in the height of these waves after treatment The elevation in the height of the T waves in this case may be associated with the increase in oxy-

5,320,000 per cubic millimeter, the reticulocyte count had dropped to 0.1 per cent, and the total cell volume was 43.5 per cent The patient's color was normal, and she was entirely symptom free She was instructed to continue taking 400 mg of ascorbic acid daily and was also given a prescription for methylthionine chloride (0.3 Gm by mouth once daily) should she become noticeably cyanotic again The patient's course has been followed for one year by correspondence with her and with the physician in the plant where she had been employed The methemoglobin content of her blood as measured on several occasions was approximately 0.7 Gm per hundred cubic centimeters, and there have been no periods of cyanosis She has faithfully maintained the high ascorbic acid intake and at no time has resorted to use of methylthionine chloride

*Laboratory Studies on Patient's Blood*—In an effort to determine the cause of idiopathic methemoglobinemia, a series of simple in vitro experiments were performed on the patient's blood before and after ascorbic acid therapy The results of these procedures may be observed in the chart

TABLE 2—Hematologic Data Before and After Ascorbic Acid Therapy

Date	Methemoglobin, Gm per 100 Cc	Hemoglobin Oxygen, Gm per 100 Cc	Total Hemoglobin, Gm per 100 Cc	Methemoglobin, per Cent of Total Hemoglobin	Total Cell Volume, per Cent	Ascorbic Acid		Blood Count		
						Plasma, Mg per 100 Cc	Urine, Mg per 24 Hr	Red Blood Cells, Millions per Cu Mm	White Blood Cells, Thousands per Cu Mm	Reticulo cytes, per Cent
11/ 4/43	3.90	11.60	15.50	25.2				5.46	7.0	1.8
11/ 6/43	3.80	11.10	14.90	25.5	44.7			5.58	6.8	
11/ 9/43	4.20	10.95	15.15	27.7			4.8			1.4
11/12/43	4.30	13.90	18.20	23.6		0.40	7.3			
11/15/43	4.40	13.20	17.60	25.0	43.5	0.51	8.7	5.39	8.5	0.1
11/16/43	Started ascorbic acid treatment—400 mg per day									
11/17/43	3.10	15.00	18.10	17.1						0.8
11/18/43	2.50	15.20	17.70	14.1		1.18	67.8	5.39	7.4	1.0
11/19/43	2.40	16.45	18.85	12.7			174.2			
11/20/43	2.35	15.80	18.15	13.0		1.58	158.4			
11/21/43							187.0			
11/22/43	2.10	16.00	18.10	11.6						
(0.30 a m)*	2.30	14.60	16.90	13.6		1.58	327.7			
11/23/43 (11.00 a m)	0.20	17.42	17.62	1.1						
11/23/43 (3.00 p m)	0.40	—	—	—						
11/24/43	0.65	16.85	17.50	3.7						
11/25/43	0.60	14.70	15.30	3.9						
11/26/43	1.03	15.70	16.73	6.2	43.5			5.32		0.1

\* Intravenous injection of 7 cc of 1 per cent solution of methylthionine chloride

hemoglobin concentration in the blood The effect of anoxemia, due to decreased atmospheric oxygen tension, on T waves is well known<sup>20</sup> In addition, similar alterations have been observed by Yonemoto<sup>21</sup> in electrocardiograms taken on rabbits after the blood had been treated with nitrite to produce 68 to 84 per cent methemoglobin

The methemoglobin started to rise again (table 2) a few hours after methylthionine chloride had been given The day after this treatment her blood contained 0.65 Gm per hundred cubic centimeters, or 3.7 per cent methemoglobin At the time of her discharge from the hospital two days later the methemoglobin content of her blood was 6 per cent and the red blood cell count

19 Hauschild, F Die Wirkung des Katalysins (Thionin) bei der Methemoglobinvergiftung, Arch f exper Path u Pharmakol 184 458-467, 1937

20 White, M S Effect of Anoxia in High Altitude Flights on the Electrocardiogram, J Aviation Med 11 166-180 (Dec) 1940

21 Yonemoto, G Electrocardiogram During Methemoglobinemia Produced by Injection of Sodium Nitrite, J Orient Med 35 117-126, 1941

Samples of the patient's blood taken on different days were allowed to remain in a test tube at room temperature, and determinations of methemoglobin were made at intervals of three to twelve hours Repeated analyses over periods of twenty-four to seventy-two hours failed to demonstrate any significant change in the methemoglobin concentration This finding is in contrast to changes that occurred in normal blood to which sodium nitrite had been added to produce methemoglobin Normal blood, with intact red cells, methemoglobinized to approximately 8 Gm per hundred cubic centimeters by the addition of 0.31 mg sodium nitrite per cubic centimeter lost most of its methemoglobin in a twenty-four hour period (section A in the chart) The rate of conversion of methemoglobin to hemoglobin at room temperature in the normal nitrated blood samples which were analyzed during this study averaged 0.3 Gm per hundred cubic centimeters per hour The reduction of methemoglobin in hemolyzed normal blood also occurs at a rapid rate Within seventy-two hours there was no change in the methemoglobin content of the patient's hemolyzed blood (section B in the chart)

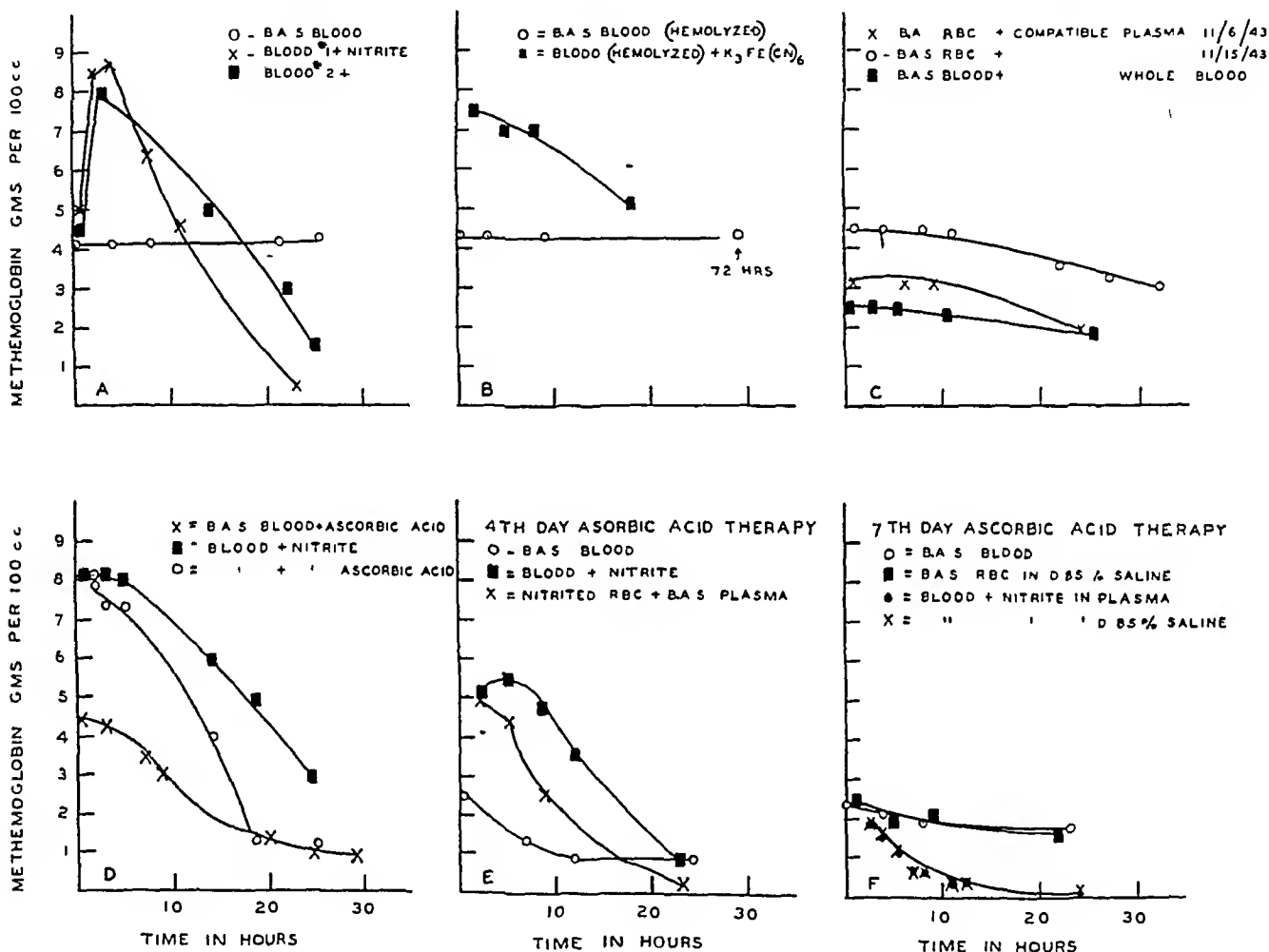
The next experiment concerned the influence of plasma of another source on the patient's corpuscular

methemoglobin content. The formed elements of the patient's blood were separated by centrifugation, and the plasma was drawn off and replaced with an equal amount of compatible plasma. There was practically no change in the methemoglobin levels during the first eight to ten hours in two separate tests. A reduction did take place in both tests during the tenth to twenty-fifth hours, but the rate of conversion did not approach that which occurs in normal nitrated blood. The compatible plasma contained 1.69 mg per hundred cubic centimeters of ascorbic acid in comparison with the patient's plasma, which contained 0.4 and 0.5 mg. During the twenty-four hour period, the erythrocytes in contact with compatible plasma lost approximately

1.3 Gm of methemoglobin per hundred cubic centimeters of blood (section C in the chart).

Compatible whole blood was then added to the patient's whole blood, which diluted the amount of methemoglobin by one half at the onset of the experiment. The methemoglobin concentration of the blood mixture was reduced from 2.5 to 1.9 Gm per hundred cubic centimeters in twenty-three hours, which is much less than the reduction to be expected with nitrated blood.

The effectiveness of ascorbic acid as a reducing agent was studied on both normal blood treated with sodium nitrite and on the patient's blood. To the nitrated blood containing 8.5 Gm methemoglobin per hundred cubic



In vitro studies at room temperature of reduction of methemoglobin in oxalated blood from patient (B A) and from a normal subject treated with methemoglobin formers. A, rate of reduction of methemoglobin in B A's blood before ascorbic acid therapy and in two samples of normal blood treated with sodium nitrite (0.31 mg per cubic centimeter of blood). B, the effect of hemolysis on the rate of methemoglobin reduction in B A's blood and in normal blood plus 1.48 mg potassium ferrocyanide ( $K_3Fe(CN)_6$ ) per cubic centimeter of blood. (The hemolyzing solution consisted of a borate buffer, pH 9.4, containing 0.3 Gm of saponin per hundred cubic centimeters.) Two tenths cubic centimeter of blood was diluted to 2 cc with the hemolyzing solution. C, the effect of compatible plasma and compatible whole blood on the reduction of methemoglobin in B A's blood. In two samples taken nine days apart the plasma was separated from the erythrocytes and replaced with an equal amount of compatible plasma. To a third sample an equal amount of compatible whole blood was added. D, the effect of addition of ascorbic acid on methemoglobin reduction in B A's blood in vitro and in normal blood treated with sodium nitrite (0.31 mg per cubic centimeter). Four-tenths mg ascorbic acid per cubic centimeter was added to the sample of B A's blood and to one half of the nitrated sample. The other half of the nitrated sample served as a control. E, rate of methemoglobin reduction in B A's blood on the fourth day of ascorbic acid therapy and in nitrated erythrocytes plus B A's plasma. Two hours after addition of sodium nitrite (0.15 mg per cubic centimeter) the plasma was separated from one half of the sample and replaced with an equal volume of B A's plasma. F, seventh day of ascorbic acid therapy. Rate of methemoglobin conversion of B A's blood and a portion of her blood in which the plasma has been replaced with an equal volume of 0.85 per cent sodium chloride solution, also, comparison of normal nitrated blood (0.08 mg sodium nitrite per cubic centimeter) in which the plasma from one half of the sample was separated and replaced with an equal volume of 0.85 per cent sodium chloride solution.

centimeters and to the patient's blood were added 0.4 mg of ascorbic acid per cubic centimeter of blood. This amount was stoichiometric for the methemoglobin content of the nitrated blood and a two-fold excess for the patient's blood, it also represented fifty times the amount of ascorbic acid ordinarily present in the plasma. The methemoglobin in the patient's blood sample was rapidly converted to hemoglobin, and the rate of methemoglobin reduction in the nitrated sample was accelerated (section *D* in the chart).

The next series of test tube experiments were conducted on the patient's blood on the fourth day of ascorbic acid therapy. At this time analysis immediately after withdrawal of venous blood showed that the methemoglobin content was 2.5 Gm per hundred cubic centimeters, a drop of 1.9 Gm in four days of treatment. When this blood sample was allowed to stand in a test tube, the methemoglobin concentration continued to fall to 0.9 Gm per hundred cubic centimeters in twenty-four hours. During this same twenty-four hour period in vivo methemoglobin concentration dropped only 0.1 Gm per hundred cubic centimeters.

The relative effectiveness of B. A.'s plasma in reducing the methemoglobin of nitrated blood was compared, after four days of vitamin therapy, with that of normal plasma. A sample of nitrated blood was divided into equal portions and the plasma of one portion replaced with the patient's plasma. Unfortunately, the oxidation reaction of the nitrite was incomplete when the plasma was separated for replacement, and methemoglobin continued to increase in the control sample. Taking this factor into account, the rate of reduction of methemoglobin continued at very nearly the same rate in both samples. The ascorbic acid levels for the two plasma samples were 1.2 mg per hundred cubic centimeters for the patient and 1.7 mg for the control (section *E* in the chart).

The role of plasma in methemoglobin reduction was next studied by comparing the effectiveness of the patient's plasma on the seventh day of therapy with that of isotonic solution of sodium chloride. Half of a blood sample from the patient was centrifuged and the plasma replaced with 0.85 per cent sodium chloride solution. The other half was used as the control. Measurements were then made of the reduction rate of the methemoglobin in each preparation for a period of twenty-four hours. The methemoglobin disappeared at the same rate in both samples. A second test was made with normal nitrated blood which was similarly handled. The conversion of methemoglobin to the reduced form again progressed at nearly the same rate when the cells were suspended in plasma or in sodium chloride solution (section *F* of the chart). In addition, the plasma was removed from a sample of the patient's blood, and twenty-eight hours later the cells were made up to the former volume with sodium chloride solution. A determination made immediately revealed only a small quantity of methemoglobin.

#### COMMENT

These experiments indicate that before ascorbic acid therapy the patient's blood had little or no power to reduce methemoglobin to hemoglobin in vitro. This is in contrast to the action of normal nitrated blood, in which methemoglobin was reduced at the average rate of 0.3 Gm per hundred cubic centimeters per hour. The separation of the patient's erythrocytes and

the addition of compatible plasma containing a high normal amount of ascorbic acid (1.7 mg per hundred cubic centimeters) caused a reduction in methemoglobin of only 1.3 Gm over a period of twenty-four hours. The delayed onset of reduction on the addition of compatible plasma suggests that a transfer of a reducing substance into the erythrocytes may have taken place. After four days of ascorbic acid therapy, the methemoglobin content of the patient's blood in vitro was reduced 1.6 Gm per hundred cubic centimeters within twenty-four hours. The patient's plasma at this time contained 1.2 mg of ascorbic acid per hundred cubic centimeters. Since, stoichiometrically, 10 mg of ascorbic acid per hundred cubic centimeters, or eight times the concentration present in the plasma, would be required to reduce 1.6 Gm of methemoglobin per hundred cubic centimeters, it becomes apparent that either another reducing system has been activated or the ascorbic acid itself is acting catalytically. The equal rates of disappearance of methemoglobin from the erythrocytes of normal nitrated blood when suspended in their own plasma or when suspended in a 0.85 per cent solution of sodium chloride indicate that the constituents of the plasma are not primarily responsible for the conversion of methemoglobin to hemoglobin. This is emphasized by the repetition of this action when the patient's erythrocytes were suspended in an isotonic solution of sodium chloride on the seventh day of ascorbic acid therapy, at which time the patient's plasma contained 1.58 mg of ascorbic acid per hundred cubic centimeters. The patient's red cells probably contained a comparable concentration of ascorbic acid.

These experiments suggest that the conversion of methemoglobin to hemoglobin is dependent on the reducing systems present within the red cell. Cox and Wendel<sup>22</sup> were of the opinion that the reduction of methemoglobin was mainly, if not entirely, a function of the enzyme system contained within the erythrocyte. In the present case a partial failure of one of the reducing systems within the erythrocyte was suspected. By elevating the ascorbic acid content of the blood to unusually high levels, the defective reducing system was partially replaced or reactivated, and the methemoglobin content of the blood was reduced, both in vivo and in vitro. The reducing mechanism was still imperfect, because a high ascorbic acid intake (over 400 mg per day) did not reduce

<sup>22</sup> Cox, W. W., and Wendel, W. B. The Normal Rate of Reduction of Methemoglobin in Dogs, *J Biol Chem* **143** 331-340 (April) 1942.

the methemoglobin level below 0.5 to 0.6 Gm per hundred cubic centimeters. Although the patient's methemoglobin concentration was temporarily reduced to 0 after the intravenous injection of methylene blue, it then leveled off at about 1.0 Gm per hundred cubic centimeters, which is approximately eight to ten times the average concentration found in a normal person.<sup>23</sup> This failure to reduce the methemoglobin concentration to normal levels may be noted in 4 other patients with idiopathic methemoglobinemia successfully treated with ascorbic acid. In no case did the methemoglobin level drop to normal, but each remained at a concentration between 6 to 11 per cent of the total pigment.

Judging from the experience of the small number of patients treated, it appears that a high concentration of ascorbic acid in the blood will control methemoglobinemia of idiopathic origin. The plasma levels of ascorbic acid which were recorded in 3 cases, including this one, were, before treatment 0.19,<sup>13</sup> 0.31<sup>14</sup> and 0.40 to 0.51, mg per hundred cubic centimeters (this case). After ascorbic acid therapy was initiated and before a reduction in the methemoglobin content had become noticeable, these levels had risen to 0.46, 1.17 and 1.24, mg per hundred cubic centimeters, respectively. In the case reported by King, Gilchrest and White, the methemoglobin in the circulating blood began to increase when the plasma level of ascorbic acid had dropped to 0.61 mg per hundred cubic centimeters after the discontinuation of ascorbic acid therapy.

In normal blood, ascorbic acid probably does not play an essential role in the maintenance of hemoglobin in a functionally active state. For example, there are no known reports of methemoglobinemia among persons with as low plasma contents of ascorbic acid as occur in scurvy. However, from the evidence presented in this case and from several reports in the literature it would appear that there is a concentration of ascorbic acid in the blood that is critical in the treatment of methemoglobinemia of idiopathic origin.

The methemoglobin concentration is probably regulated by the various oxidation-reduction

systems present in the red blood corpuscle. Warburg and Christian<sup>24</sup> have shown with their experiments on the various enzyme systems that methemoglobin is reduced by the system hexosemonophosphate - dehydrogenase - triphosphopyridinenucleotide. The oxidation-reduction potential of the methemoglobin-hemoglobin system of the horse, when the concentration of oxidant and reductant are equal, is +0.139 volt at pH, 7.0 at 30°C.<sup>25</sup> Normally, human blood contains approximately 1 per cent of total hemoglobin as methemoglobin. By computation<sup>26</sup> the potential for 1 per cent methemoglobin and 99 per cent hemoglobin is about 0 volt. Our patient's blood before treatment contained from 25 to 50 per cent methemoglobin as measured on widely separated occasions. The calculated potential for 25 per cent methemoglobin and 75 per cent reduced hemoglobin is +0.11 volt. On the basis of this calculation it necessarily follows that the normal reducing systems were inactive.

The following data reported in the literature may be relevant to this concept. The various normal values recorded for the potential of whole blood in vitro range from +0.110 to +0.200 volt, depending on the procedure used for measuring the potential.<sup>27</sup> The presence of intact erythrocytes has but slight influence on the potential of plasma or serum. However, when the blood is hemolyzed there is a definite drop in potential, which indicates that the potential within the normal red cell is much lower than that in the plasma.<sup>28</sup> On the other hand, hemoglobin is converted to methemoglobin when added to plasma. In the circulating blood as much as 40 per cent of injected hemoglobin may be converted to methemoglobin over a period of twenty-four to forty-eight hours.

24 Warburg, O., and Christian, W. Ueber Aktivierung der Robinschen Hexose-Mono-Phosphorsäure in roten Blutzellen und die Gewinnung aktivierender Fermentlösungen, *Biochem Ztschr* **242** 206-227 (Nov 17) 1931.

25 Taylor, J. F., and Hastings, A. B. Oxidation-Reduction Potentials of the Methemoglobin-Hemoglobin System, *J Biol Chem* **131** 649-622 (Dec) 1939.

26  $E_h = E_o \frac{0.060}{n} \times \log \frac{\text{oxidant}}{\text{reductant}}$  (Bodansky, M. Introduction to Physiological Chemistry, New York, John Wiley & Sons, Inc 1938).

27 Meier, L. Die Bestimmung des Redoxpotentials im Blut (in vitro) und die Beeinflussung durch Zuführen sogenannter Redoxsubstanzen, *Biochem Ztschr* **303** 32-39 (Nov) 1939. Oivine, I. A. Potential oxydo-reducteur ( $E_h$ ) du sang, *Bull biol med exper*, U R S S **3** 542-544, 1937.

28 Oivine, I. A. Controversial Problems of the Oxidation-Reduction Potential of the Blood, *Bull biol med exper*, U R S S **7** 344-347, 1939.

23 Paul, W. D., and Kemp, C. R. Methemoglobin A Normal Constituent of Blood, *Proc Soc Exper Biol & Med* **56** 54-55 (May) 1944. Sievers, R. F., Lawton, A. H., Skoog, F., Neal, P. A., von Oettingen, W. F., Stump, R. L., and Monaco, A. R. A Medical Study of the Effect of TNT on Workers in a Bomb and Shell Loading Plant, *Public Health Bulletin* 291, United States Treasury Department, Public Health Service, 1945.

On the basis of this evidence, the following hypothesis is offered as a suggestion for the mechanism involved in idiopathic methemoglobinemia

Methemoglobin is constantly being produced in the circulating blood. In the case of idiopathic methemoglobinemia the reducing systems within the erythrocyte which normally keep methemoglobin at low concentrations are inactive or at reduced activity. In the absence of these reducing systems the potential of the erythrocyte will tend to increase as the diffusible oxidation-reduction systems of the plasma enter the cell, resulting in the production of methemoglobin. The extent of methemoglobin formation will be a function of the degree to which the normal reducing systems are lacking in the erythrocyte and of the rate at which the plasma constituents will diffuse into the cell. In the treatment of idiopathic methemoglobinemia with large doses of ascorbic acid, the high concentrations of ascorbic acid within the erythrocyte serve as a substitute for the missing reducing system.

#### SUMMARY

Medical and laboratory tests and observations were made on a 19 year old woman with methemoglobinemia dating from birth. There was no evidence of gastrointestinal disturbance, and no other member of her family had cyanosis.

The observations reported by others that the oral administration of ascorbic acid diminishes methemoglobinemia and cyanosis were confirmed. It was found that relatively high plasma concentrations of ascorbic acid were required to be effective and that the methemoglobin was not reduced to the levels found in normal circulating blood. Complete and temporary reduction of methemoglobin after an intravenous injection of methylene blue with return of methemoglobin concentration to approximately 6 per cent while the patient had a high ascorbic acid intake was demonstrated.

In vitro experiments were conducted prior to and during treatment in an attempt to determine the mechanism of idiopathic methemoglobinemia. From results obtained in these experiments a hypothesis was formulated to explain this mechanism.

# STUDY OF WATER AND HEAT LOSS FROM THE RESPIRATORY TRACT OF MAN

METHODS I A GRAVIMETRIC METHOD FOR THE MEASUREMENT OF THE RATE OF WATER LOSS, II A QUANTITATIVE METHOD FOR THE MEASUREMENT OF THE RATE OF HEAT LOSS

GEORGE E BURCH, M D

NEW ORLEANS

In any study of water loss from the human body it is necessary to measure that which leaves the respiratory system. Methods have been described, but they are either inaccurate or cumbersome. It is beyond the scope of this paper to review the methods used in the past to measure the water loss through the pulmonary system, many of these are referred to in several excellent discussions on insensible perspiration.<sup>1</sup> Galeotti and his associates<sup>2</sup> and Weyrich<sup>3</sup> used bottles of sulfuric acid or calcium chloride to trap the expired water and measure gravimetrically the water collected. These are not simple procedures, and their accuracy is not well established. The observers did not control the conditions of the air inspired. The paper by Galeotti and Signorelli<sup>2a</sup> included a review of some of the early methods used to measure expired water. Loewy and Gerhartz<sup>4</sup> measured the temperature of the air expired but not the water loss from the lungs.

This is the thirteenth paper from the Laboratory of Tropical Physiology

Aided by a grant from the Rockefeller Foundation and the Helis Institute for Medical Research

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana

1 (a) Soderstrom, G F, and Du Bois, E F. Clinical Calorimetry XXV. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch Int Med **19** 931 (May) 1917. (b) Benedict, F G, and Root, H F. Insensible Perspiration Its Relation to Human Physiology and Pathology, *ibid* **38** 1 (July) 1926. (c) Newburgh, L H, and Johnston, M W. The Insensible Loss of Water, *Physiol Rev* **22** 1, 1942. (d) Hill, L. The Science of Ventilation and Open Air Treatment, London, His Majesty's Stationery Office, 1919.

2 (a) Galeotti, G, and Signorelli, E. Ueber die Wasserbilanz während der Ruhe und bei der Anstrengung im Hochgebirge, *Biochem Ztschr* **41** 268, 1912. (b) Galeotti, G. Ueber die Ausscheidung des Wassers bei der Atmung, *ibid* **46** 173, 1912.

3 Weyrich, W. Beobachtungen über die unmerkliche Wasserausscheidung der Lungen und ihr Verhältniss zur Hautperspiration, Dorpat, E J Karow, 1865.

4 Loewy, A, and Gerhartz, H. Ueber die Temperatur der Expirationsluft und der Lungenluft, *Arch f d ges Physiol* **155** 231, 1914.

The method of Benedict and Benedict,<sup>5</sup> using chemical absorption, is rather cumbersome and relatively inaccurate. Christie and Loomis<sup>6</sup> employed an ingenious and accurate method for measuring the water vapor pressure of expired air. The method cannot be employed to determine accurately the quantity of water loss from the lungs. In an excellent and more recent paper Seeley<sup>7</sup> described a method using anhydrous magnesium perchlorate in U tubes to collect and weigh the expired water. Not only is this method cumbersome, but its accuracy is not fully established. It was intended and was used by Seeley with success for the measurement of relatively small samples (1 to 2 liters) of expired air. In another study<sup>8</sup> I like Benedict and Benedict<sup>5</sup> Newburgh and Johnston<sup>1c</sup> and others, employed a large sensitive balance to measure water loss from the lungs and skin. This method is relatively inaccurate and not applicable to certain types of studies.

In order to study water and heat loss from the lungs it became necessary to develop an accurate, dependable and practical method for measuring water loss. The method was developed further to measure heat loss simultaneously with water loss in a manner so that ambulatory and hospital patients as well as normal subjects could be studied in large numbers and at frequent intervals.

To facilitate presentation, the paper is divided into two parts, describing (1) the method for measuring water loss gravimetrically and (2) the

5 Benedict, F G, and Benedict, C G. Perspiratio insensibilis. Ihr Wesen und ihre Ursachen, *Biochem Ztschr* **186** 278, 1927.

6 Christie, R V, and Loomis, A L. The Pressure of Aqueous Vapour in the Alveolar Air, *J Physiol* **77** 35, 1932.

7 Seeley, L E. Study of Changes in the Temperature and Water Vapor Content of Respired Air in the Nasal Cavity, *Tr Am Soc Heat & Vent Engin* **46** 259, 1940.

8 Burch, G E. A Method for Measuring Small Amounts of Weight Loss in Man, *Am J M Sc*, to be published.

method for measuring heat loss from the respiratory tract.

# I A GRAVIMETRIC METHOD FOR THE MEASUREMENT OF EXPIRED WATER

The apparatus and method developed to measure quantitatively the expired water are illustrated diagrammatically by figure 1. The apparatus consists essentially of three parts (1) two meters for measuring the volume of air circulated through the lungs and collecting coils, (2) aluminum collecting coils and (3) a system of rubber tubing with necessary heater, flutter valves and mouthpiece to direct the flow of air.

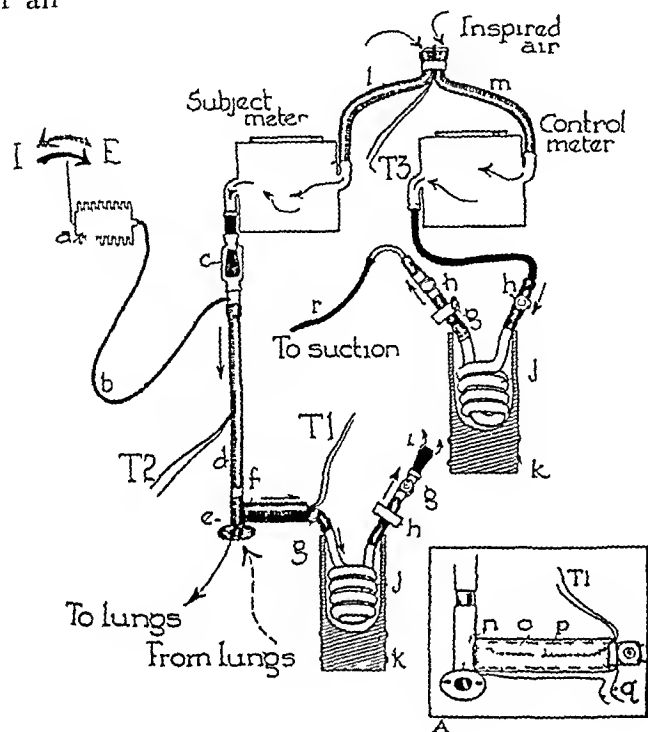


Fig 1—A schematic representation of the apparatus employed to measure the rate of water loss from the respiratory tract. The mouthpiece (c) is placed in the subject's mouth, and his nose is clipped closed. On breathing he inspires room air through tubing (1). The air passes through the "subject meter," where its volume is recorded. It then passes through the flutter valve and housing (c) and through rubber tube (d) into his lungs. On expiration the air passes out through the side tubing in the mouthpiece through the heated rubber efferent tube (insert A) into aluminum coil (j) and out through the trap (h), stopcock (g) and flutter valve (i) into the atmosphere.

Copper—constantan thermocouples ( $T_1$ ,  $T_2$  and  $T_3$ ) are used to record the temperature of the inspired and expired air. The brass bellows (a) with pivoted lever is connected to the tubing (d) by means of rubber tubing (b) and indicates mechanically the phases of respiration.

Room air is drawn by means of a suction system through rubber tubing (m) and through the control meter, where its volume is recorded. It is then drawn through aluminum coil (j), through the trap and then out into the suction system by means of tubing (r).

Insert A shows the nature of the construction of the electrically heated efferent tubing carrying the expired air to the aluminum coil. A wall (n) is constructed in each mouthpiece to prevent the inspired and expired air from mixing outside the subject's mouth.

1 The meters are ordinary commercial test gas meters which measure the volume of air flow under low pressure to an accuracy of about 30 cc. All air that circulates through the lungs and coils passes through the meters so that the volume and rate of circulation of air may be determined.

2 Aluminum coils are constructed and employed essentially as described for the coils used for measuring water loss from the skin.<sup>9</sup> The coils are made to weigh less than 200 Gm, so that they can be weighed on an ordinary analytic balance. The internal diameter of the aluminum coils is about 16 mm and the walls about 0.7 mm thick. The length of tubing in each coil is about 160 cm. There is no kinking of the tubing, and the diameter of the coils is small enough for them to be placed on an ordinary analytic balance. A finished coil is shown in figure 2. Each open end of the coil is connected by rubber tubing to an aluminum stopcock, to make it possible to isolate the lumen of the collecting coil from the

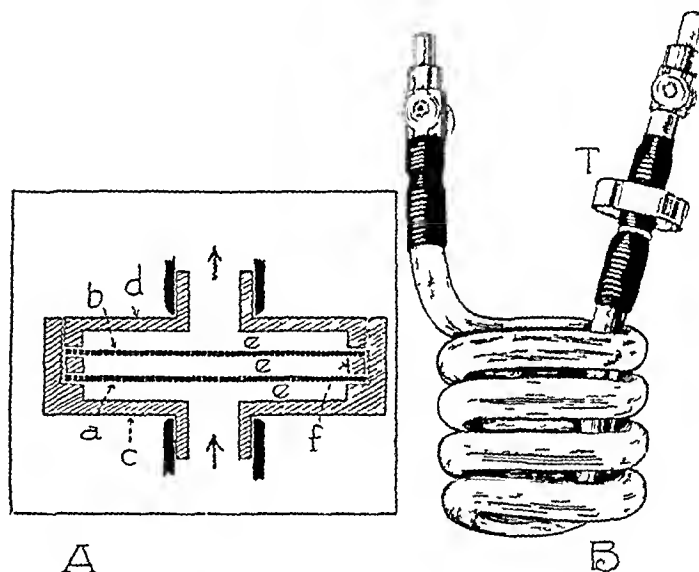


Fig 2—A schematic representation of the aluminum collecting coils. Insert A shows the details of construction of the trap (T) used to prevent the escape of frozen water on expiration. Parts a and b are fine meshed brass filters, e, e' and e'' are air spaces between the filters which allow free circulation of the expired air.

atmosphere. By carefully varying the amount of rubber tubing and aluminum tubing slightly, all coils are made to weigh about the same (within a few milligrams) to facilitate weighings.

A metal filter (insert A, fig 2) is placed just proximal to the stopcock guarding the exit from the coils, to prevent any of the condensed frozen expired water from being blown out of the coils.

9 Neumann, C., Cohn, A. E., and Burch, G. E. A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas, with Results for Finger Tip, Toe Tip, and Posterior-Superior Portion of the Pinna of Normal Resting Subjects, *Am J Physiol* 132:748, 1941.

This filter consists of a short broad thin-walled cylindric aluminum housing and two layers of 100 mesh per square inch brass screen. The two layers of screen filter are kept apart from each other by means of a metal ring (*f*, insert *A*, fig 2). The diameter of the housing is 4.0 cm and the length 1.0 cm. The large diameter reduces the resistance to the flow of air through the housing, and the double layer of filter insures complete trapping of the snow.

3 The rubber tubing, flutter valves and mouthpiece are connected as shown in figure 1. A nichrome heater (*o*, insert *A*, fig 1) surrounds the efferent tube (*p*) leading from the mouthpiece to the subject collecting coil<sup>10</sup> to maintain the walls of this efferent tubing at a temperature of 92 F (33.4 C) to prevent condensation of expired water within its walls. A rheostat is connected in series with the heater to vary the heater temperature whenever the environmental temperature is varied.

In use, the previously dried (by fanning with an electric fan and by wiping the external surface and drawing air through the interior) and weighed coils are placed in a thermos jar and iced with chips of solid carbon dioxide (fig 1). This procedure cools the coils to about -70 C. The coils are then connected to the meters, the patient and the air suction lines as indicated by figure 1. The room in which the studies are conducted is air conditioned. The subject, who has rested a given period, inserts the mouthpiece (such as is used for ordinary clinical measurements of metabolic rate) in his mouth and adjusts his chair and the apparatus so that he is comfortable and well relaxed. He is instructed to breathe through his nose while all stopcocks are opened and air lines through the subject coil made patent. The nose is then closed with a clip, and timing with a stopwatch is started simultaneously. The subject then inhales air from the room through the subject meter (fig 1) into his lungs, out through the warm efferent tube (*p*) and through the subject coil (*j*), where the expired water condenses, the dry air escaping into the atmosphere. This procedure is continued for a period of five minutes.

Simultaneously with the collection of the expired water from the subject, an equal volume of room air is drawn through the room meter and through the room coil (*j*), the dry room air escaping into the vacuum system providing the suction. The intake openings for the subject

meter and the room meter are placed adjacent to each other in order to insure an entrance of similar room air into both systems, that of the patient and that of the control, or room air, system. After a given period (accurately recorded) of study, the stopcocks guarding the collecting coils are closed. The coils are dried by fanning and wiping and are weighed again. The gain in weight represents the quantity of water collected over the known period of time and after known volumes of air have irrigated the respiratory tract. From the known quantities, the subject's weight and height, the grams of water collected and the time, the rate of water loss is calculated, expressed in grams per square meter of body surface per ten minutes.

The number of grams of water collected in the subject coil represents (1) the water in the room air inspired and (2) the water lost from the respiratory tract. The water collected in the room coil represents the water contained in the room air inspired. The difference between the number of grams of water collected in the subject coil and that collected in the room coil represents the quantity of water lost from the respiratory tract.

#### CALIBRATION AND TESTING OF APPARATUS AND METHOD

1 *Accuracy of the Method*—To determine the accuracy of the method a Kjeldahl connection bulb containing water was placed in the air line of the subject coil and meter in the relative position occupied by the subject. Air was drawn through the subject meter, through the connection bulb containing a known amount of water and then through the subject coil. Simultaneously an equal volume of room air was drawn through the room meter and coil. By weighing the coils and connection bulb before and after this procedure, it was possible to determine the accuracy of the method for collecting expired water. It was possible to vary the quantity of water lost by the connection bulb by heating the bulb.

The results are shown in the table. The mean error is -0.27 per cent and the extremes +1.25 and -1.27 per cent. The results were not influenced by the quantity of water collected within the limits of amounts involved when subjects were studied. More rapid rates of water loss were not studied. Variations in the rate of air flow within the limits encountered when studying subjects did not influence the accuracy of the method.

2 *Completeness of Collection of Water by a Single Collecting Coil*—In order to determine the completeness with which the water is trapped by the subject coil, two coils were connected in series and iced with solid carbon dioxide. Room

<sup>10</sup> The term "subject coil" is employed to indicate the aluminum collecting coil used to trap the expired water and "room coil" to indicate the collecting coil used to measure the water content of an equal volume of room air.

air was drawn through the coils, or a subject expired through the coils. It was found that the first coil through which the moisture-laden room air or expired air entered trapped the moisture almost completely. For example, when the quantity of water trapped by the first coil was about 400 mg, the maximum amount of water collected by the second collecting coil in the series did not exceed 4 mg. When the first coil collected about 1,500 mg of water, the second coil collected a maximum of 17 mg. These figures would seem to indicate that when quantities of water collected

error not exceeding 2 mg and usually amounting to less than 1 mg. This is a surprisingly small error considering the surface area of the coils, the method of drying and the accuracy of the balance ( $\pm 0.1$  mg) used for the weights.

**5 Resistance to Air Flow Through the Coils**—The length of the aluminum tubing and the diameter of the lumen has increased the friction to the flow of air from the respiratory tract on expiration. By placing a T tube in the system of tubing near the mouthpiece and connecting this to a mercury manometer, it was found that the pressure of expiration on quiet respiration averaged  $+36$  mm of water (26 mm of mercury), the extremes being 30 and 40. The pressure on inspiration was of essentially the same magnitude but negative. When inspiration or expiration was sudden or jerky, the pressure changes were slightly greater.

**6 Condensation of Moisture in the System Other than in the Collecting Coils**—The first group of experiments showing the accuracy of the method indicated the lack of any appreciable loss of water by condensation in the system other than in the collecting coils. The heater around the efferent tubing prevented any such loss. As will be seen, a thermocouple placed within the efferent tube made it possible to be sure that sufficient warmth of the walls of the efferent tube existed prior to the start of any study in order to prevent condensation on its walls. Furthermore, segments of glass tubing were placed in various places within the system. The failure of the walls of the glass tube to be clouded by water condensing on their surfaces after prolonged breathing through the system indicated that no large quantities of water were lost by condensation within the tubings.

*The Accuracy of the Proposed Method for Measuring the Rate of Water Loss From the Respiratory Tract*

Test No	Known Water Loss, Gm	Water Collected, Gm	Error, Gm	Error, per Cent
1	0.7943	0.7899	-0.0044	-0.55
2	1.0578	1.0553	-0.0025	-0.24
3	0.7657	0.7646	-0.0011	-0.14
4	0.7653	0.7602	-0.0051	-0.67
5	0.7064	0.7152	+0.0088	+1.25
6	0.8163	0.8112	-0.0051	-0.62
7	0.8596	0.8656	+0.0060	+0.70
8	1.0781	1.0730	-0.0051	-0.47
9	1.0821	1.0743	-0.0078	-0.72
10	0.8337	0.8231	-0.0106	-1.27
Mean	0.87593	0.87324	-0.0027	-0.27
Maximum	1.0821	1.0743	+0.0088	+1.25
Minimum	0.7064	0.7152	-0.0106	-1.27

are near 1 Gm or less the error due to incomplete removal of the water from the expired air is less than 1 per cent. It will be seen in the papers to follow that in the usual experiment the water collected in any one collecting coil rarely exceeds 1 Gm.

**3 The Control of Water in Room Air**—The accuracy of the method depends on the accuracy with which the water in the room air is measured. For example, room air is drawn through the two meters and collecting coils simultaneously and through the orifices of two rubber tubes placed adjacently (fig 1). It is possible that the water contents of air entering each differ. To test this possibility, room air of equal volume was drawn through a separate meter and coil simultaneously.

In a typical experiment, one coil collected 0.4686 Gm of moisture from the room air, and the other collected 0.4685 Gm from an equal volume of room air. These amounts indicate that the method employed for controlling the moisture in the room air is satisfactory.

**4 Errors Involved in Drying and Weighing the Collecting Coils**—The process of drying the outside of the coils by wiping and fanning and of weighing, icing them, drying them again by wiping and fanning and then weighing them again must entail certain errors. As a test, several coils were put through the process outlined in the preceding sentence. The results showed an

## II METHOD FOR MEASURING THE RATE OF HEAT LOSS FROM THE RESPIRATORY TRACT

With only relatively slight modifications, the method just described for determinations of water loss may be used to measure the heat loss from the lungs simultaneously with the water loss.

Heat is lost from the lungs by (1) evaporation of water, (2) warming of inspired air (convection) and (3) decomposition of carbonic acid in solution to carbon dioxide gas with expiration. The first is measured by the method just described, therefore making it necessary to measure only two other factors, the kilogram calories lost by (1) warming inspired air and (2) the excretion of carbon dioxide.

**The Method for Measuring Heat Loss by Warming of Inspired Air (Convection)**—To measure the heat loss by warming of inspired air

thermocouples were placed in the efferent tube ( $p$ ), in the afferent tube ( $d$ ) and at the site of entrance of the room air into the subject meter (fig 1). These made it possible to determine with a potentiometer (accurate to 0.1 degree [C]) the temperature of the inspired and expired air. The subject meter recorded the volume of inspired air in a known period of time. From the temperature of the expired air and from the number of grams of water removed from the expired air, it was possible to determine the mass of an expired as well as its specific heat. With these factors known it was possible to calculate the rate of heat loss by convection.

The fine wire used for the thermocouples (copper-constantan) made it possible to record the temperature of the expired air during expiration as the expired air passed over the thermocouple junction. The heat from the nichrome heater around the efferent tube did not interfere with the recording accurately of the temperature of the expired air, because of the heater's being outside a thick-walled rubber tubing (rubber is

equilibrium to be reached, but to avoid errors it is preferable to wait at least two minutes.

*The Measurement of Heat Loss by Excretion of Carbon Dioxide*—The excretion of carbon dioxide was measured by having the subject breathe in a Benedict-Roth type of clinical machine for measuring the basal metabolic rate immediately after collecting the expired water, measuring inspired and expired air temperatures and so on. This was done without allowing the subject to move from his previous sitting position used for measuring the expired water. Since the subjects were all normal adults on a mixed diet the rate of liberation of carbon dioxide was calculated from the rate of absorption of oxygen as recorded by the B M R machine. This calculation was made by using a respiratory quotient of 0.83, that is,  $\text{CO}_2 \text{ (liters)} = 0.83 \text{ O}_2 \text{ (liters)}$ .

At the same time the recorded metabolic rate (M R), not basal metabolic rate (B M R), was determined. Since the subjects rested from thirty to sixty minutes in the observation room before the metabolic rate was recorded, it is fairly safe to assume that the body was in temperature equilibrium with the environment and that, therefore, the total body heat production (determined from the metabolic rate) was equal to the total heat loss. This assumption certainly is true when the subject is in heat equilibrium with his environment. From this measured heat loss it is possible then to express heat loss by all or any of the three previously mentioned components of respiratory heat loss as per cent of total body heat loss.

By measuring the subject's height and weight it is possible to correct for body size. This is done by expressing all heat loss in units of kilogram calories (large or physiologic) per square meter of surface area per ten minutes.

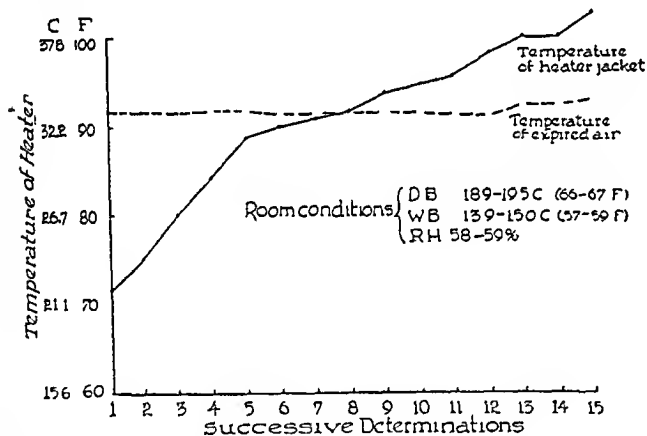


Fig 3—The influence of the temperature of the heater jacket and efferent tube (insert A, fig 1) on the temperature of the expired air. The conditions of the room (temperatures by dry bulb and wet bulb thermometers and relative humidity) are shown.

a good insulator of heat), because of the fineness of the thermocouple wire and because of the setting of the temperature of the heater at a level very near (0 to 1 C variation) the temperature of the expired air. Figure 3 shows that the temperature of the heater did not influence the recording of the expired air unless the temperature of the heater exceeded 36 C (about 96 F). For heater temperatures as low as 21 C (about 70 F) the recording of the expired air temperature was not altered.

The temperatures are recorded from two to four minutes after the subject begins to respire in the water-collecting apparatus. It does not take nearly as long as two minutes for a state of

#### MATHEMATICAL CONSIDERATION OF HEAT LOSS FROM THE RESPIRATORY TRACT

The heat loss from the respiratory tract, as previously mentioned, consists of three components. It does not include heat loss by conduction or radiation, two factors important in heat loss from the surface of the body. The loss of heat<sup>11</sup> from the lungs may be expressed as

$$H = h_E + h_C = h_{CO_2} \quad (1)$$

where

$H$  = Total heat loss from the respiratory tract

$h_E$  = Heat loss by evaporation of water from the membranes of the respiratory tract

$h_C$  = Heat loss by warming inspired air (convection), (this may be a positive number if air warmer than body temperature is inspired)

<sup>11</sup> Units for heat loss henceforth will be kilogram calories per square meter of surface area of body per ten minutes.

$h_{co}$  = Heat loss by virtue of the decomposition of  $H_2CO_3$  in solution to  $CO_2$  gas, which is expired

The heat loss by evaporation of water may be expressed as

$$h_e = \frac{0.575 W}{A} \quad (2)$$

where

$h_e$  = kilogram calory per square meter of surface area per ten minutes

$W$  = grams of water lost from the respiratory tract per ten minutes

$A$  = surface area of the subject in square meters  
The parameter 0.575 is the part of a kilogram calory necessary to vaporize 1 Gm of water at a temperature of 37.25 C

The heat lost by convection (heating of inspired air) may be expressed as

$$h_c = \frac{M (t^1 - t) S}{A} \quad (3)$$

where

$h_c$  = kilogram calory per square meter of surface area per ten minutes

$M$  = mass of air expired (in grams) in ten minutes

$t^1$  = temperature of the expired air in degrees Centigrade

$t$  = temperature of the inspired air in degrees Centigrade

$S$  = specific heat of air

$A$  = surface area of the subject's body in square meters

Equation (3) becomes (for dry air)

$$h_c = \frac{0.2404 M (t^1 - t)}{1000 A} = \frac{2404 M (t^1 - t)}{10^7 A} \quad (4)$$

The heat lost by the excretion of  $CO_2$  may be expressed at standard conditions as

$$h_{co2} = \frac{L h_v}{22.4 A} \quad (5)$$

where

$h_{co2}$  = kilogram calory per square meter of surface area per ten minutes

$L$  = liters of  $CO_2$  expired in ten minutes

$h_v$  = kilogram calory of heat absorbed per mol of  $CO_2$  gas liberated when  $H_2CO_3$  in solution is decomposed

$A$  = surface area of the subject's body in square meters

22.4 = volume of a mol of a gas under standard conditions

Equation 5 becomes

$$h_{co2} = \frac{4.7 L}{22.4 A} \quad (6)$$

From the thermochemical equations, the decomposition of carbonic acid in an infinite dilution to water and carbon dioxide is associated with the absorption of 4.7 kilogram calories for each mol of carbon dioxide liberated. The blood in the lungs is not truly an infinite dilution of carbonic acid, but for practical purposes it may be considered as such.

From equations (2), (4) and (6), equation (1) becomes

$$H = \frac{0.575 W}{A} + \frac{2404 M (t^1 - t)}{10^7 A} + \frac{4.7 L}{22.4 A} \quad (7)$$

### COMMENT

The method for measuring expired water is accurate and simple to use. It can be used in the study of subjects when exercising, sitting or lying. Variations in the conditions of the room and do not influence the results, since the water in the room air is collected and measured simultaneously with the expired water. The pressure of 30 to 40 mm of water against which the subjects must expire is an objection and may be eliminated when the proper type of aluminum tubing becomes available. That, however, is not a serious objection, since the pressure is not high and is fairly constant.

The methods used by others<sup>1,2</sup> have not been accurately calibrated and in many instances not calibrated at all. The completeness of absorption of the expired air has not been carefully determined. All of them offer a certain amount of resistance to expiration, a factor not quantitatively expressed in the published reports.

Sulfuric acid has been one of the agents frequently employed to absorb the expired moisture. It does not lend itself well for such measurements, since a relatively large volume of sulfuric acid must be used to absorb completely the moisture in the expired air. Such large volumes are difficult to weigh accurately during short time studies as well as dangerous to use.

In the use of cold aluminum coils, obstruction of the lumen by frozen water has not occurred in a single instance. Of course, it is necessary to make certain that the interior of the coils is dry and that the studies do not extend over too long a period of time. Five minute studies were conducted in observations made in the Laboratory of Tropical Physiology. As shown in figure 2, a filter was inserted proximal to the stopcock at the exit of the coil in order to prevent any of the snow or frozen water from being blown out of the coil. There has been no plugging of the filter during the studies in this laboratory.

The methods for the measurement of heat loss from the respiratory tract and the partition into the three components, (1) heat loss by evaporation of water, (2) heat loss by warming of inspired air and (3) heat loss by excretion of carbon dioxide, are not complicated. Of the three, the measurement of heat loss by evapo-

<sup>12</sup> Hill<sup>1d</sup> Galeotti and Signorelli<sup>2a</sup> Galeotti<sup>2b</sup> Weyrich<sup>3</sup> Loewy and Gerhartz<sup>4</sup> Benedict and Benedict<sup>5</sup>

ration of water is most accurate. In a group of studies, measurement of water loss from the lungs is accurate to about 0.3 per cent without altering the practicability of the measurements. The measurements of heat loss by the other two factors ( $h_c$  and  $h_{co}$ ) may be made more accurate by the use of more sensitive but less practical methods than those outlined. The accuracy of the methods presented is great enough, and the methods are still simple and practical enough for use in the study of many normal and diseased subjects. The results of such studies are presented in detail in another paper.<sup>13</sup>

It is obvious that more satisfactory measurements of heat loss can be made in a room with its temperature and relative humidity controlled, such a room being employed in studies reported

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<sup>13</sup> Burch, G. E. The Rate of Water and Heat Loss from the Respiratory Tract in Normal Subjects in a Subtropical Climate, to be published.

from the Laboratory of Tropical Physiology.<sup>14</sup> This is not necessary, however, since all the measurements can be made within an hour, during which time the atmospheric conditions of most observation rooms are constant, and it is then necessary only to measure and describe the conditions of the room during the study.

#### SUMMARY

A simple and practical gravimetric method was devised for the measurement of water loss from the respiratory tract. The mean accuracy of the method is about 0.3 per cent and the extremes  $\pm 1.3$  per cent. The use of the method was studied.

A method was devised for the measurement of heat loss from the respiratory tract. The components of the heat loss were measured separately.

Mr. G. Morgani assisted in these studies.

# RATE OF WATER AND HEAT LOSS FROM THE RESPIRATORY TRACT OF NORMAL SUBJECTS IN A SUBTROPICAL CLIMATE

GEORGE E BURCH, M D  
NEW ORLEANS'

The rate of water loss and heat loss from the lungs of man has not received much attention during the past two decades. Most of the studies were conducted in the latter part of the last century and the early part of this one.<sup>1</sup> In studies of insensible perspiration, water loss from the lungs was measured indirectly by a large sensitive balance, a method originated by Sanctorius.<sup>2</sup> More recently Seeley,<sup>3</sup> and Christie and Loomis<sup>4</sup> have studied the temperature of expired air and some aspects of expired water. Except for the early studies, there have been no detailed observations of late devoted to a quantitative measurement of expired water and to the study of factors influencing this loss. There are considerable discrepancies in the early papers. For example, Weyrich<sup>1d</sup> stated that

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital

Aided by a grant from the Helis Institute for Medical Research and the Rockefeller Foundation

1 (a) Galeotti, G, and Signorelli, E. Ueber die Wasserbilanz während der Ruhe und bei der Anstrengung im Hochgebirge, *Biochem Ztschr* **41**:268, 1912 (b) Loewy, A, and Gerhartz, H. Ueber die Temperatur der Expirationsluft und der Lungenluft, *Arch f d ges Physiol* **155** 231, 1914 (c) Benedict, F G, and Benedict, C G. Perspiration insensibilis. Ihr Wesen und ihre Ursachen, *Biochem Ztschr* **186**:278, 1927 (d) Weyrich, W. Beobachtungen über die unmerkliche Wasserausscheidung der Lungen und ihr Verhältniss zur Hautperspiration, *Dorpat, E J Karow*, 1865 (e) Rubner, M. Notiz über die Wasserdampfausscheidung durch die Lunge, *Arch f Hyg* **33**:151, 1898 (f) Galeotti, G. Wassergehalt und Temperatur der ausgeatmeten Luft, *Arch f d ges Physiol* **160**:27, 1914-1915, (g) Ueber die Ausscheidung des Wassers bei der Atmung, *Biochem Ztschr* **46** 173, 1912 (h) Loewy, A, and Gerhartz, H. Ueber die Ausscheidung des Wasser bei der Atmung, *Biochem Ztschr* **47** 343, 1912

2 Benedict, F G, and Root, H F. Insensible Perspiration. Its Relation to Human Physiology and Pathology, *Arch Int Med* **38** 1 (July) 1926 Newburgh, L H, and Johnston, N W. The Insensible Loss of Water, *Physiol Rev* **22** 1, 1942

3 Seeley, L E. Study of Changes in the Temperature and Water Vapor Content of Respired Air in the Nasal Cavity, *Tr Am Soc Heat & Vent Engin* **46** 259, 1940

4 Christie, R V, and Loomis, A L. The Pressure of Aqueous Vapour in the Alveolar Air, *J Physiol* **77** 35, 1932

he had definitely shown that expired air is completely saturated with water vapor. Galeotti,<sup>1f</sup> on the other hand, found pulmonary air at body temperature to be only partially saturated at the temperature of expired air. It is known, however, that it is impossible completely to saturate inspired air with water from the surfaces of the respiratory tract, for the water on these surfaces contains colloid and crystalloid materials. The early studies in the literature also failed to consider adequately the conditions of the inspired air, the nature of respiratory conditions of the patient and many other factors concerned with the elimination of water by respiration. Seeley,<sup>3</sup> in an excellent report, considered many of the factors influencing the loss of water by the lungs. His studies should have been extended further, to include more subjects and more quantitative data. Studies in a subtropical climate have been neglected. As was pointed out previously, it is relatively simple to measure the heat loss with an evaluation of its various components while measuring the rate of water loss from the respiratory tract.<sup>5</sup>

This report is concerned with (1) measurements of the rate of water loss from the respiratory tract of normal young adults, (2) study of factors influencing this water loss and (3) measurements of the rate of heat loss from the respiratory tract, with its partition into three main factors. All subjects lived in a subtropical climate and were studied under various conditions of room temperature and relative humidity so as to simulate tropical, desert and cool environments. It was the purpose of this study to measure these physiologic phenomena in a subject sitting quietly, not in a basal state, under known environmental conditions, the attempt being made to duplicate conditions of any man merely sitting restfully in his home.

## METHODS AND MATERIAL

The methods used for the measurements of water and heat loss from the respiratory tract have been

5 Burch, G E. A Study of Heat and Water Loss from the Respiratory Tract of Man. Methods. I. A Gravimetric Method for the Measurement of the Rate of Water Loss, II. A Quantitative Method for the Study of the Rate of Heat Loss, this issue, p 308,

described<sup>5</sup> All 107 subjects studied varied from 17 to 43 years of age unless otherwise stated Except for 4 subjects, all were less than 30 years of age and only 3 were less than 20 years (one 17 years and two 19) There were 8 older subjects (fig 1) for whom only the rate of water loss was measured The subjects were normal and experienced around laboratories and included both sexes and the white and Negro races They were eating an average American diet and were free from any mild infections The subjects were studied from two to four hours postprandially The observations were made in an air-conditioned room Unless otherwise stated, the room was comfortable to practically all subjects, that is, the temperature varied from 20 to 21.1 C (68 to 70 F) and the relative humidity from 55 to 60 per cent<sup>6</sup> The subjects who considered the room a little cool were allowed to put on a light jacket to provide comfort Any variations in the room conditions from those described will be noted

The studies were conducted in New Orleans during the months of August through December 1944 and January 1945

All subjects rested, sitting quietly from twenty to forty-five minutes, usually thirty minutes, in comfortable chairs before the observations were begun They entered into peaceful conversation with the observers and shifted in their chairs as desired They were not in a basal state The room was specially constructed to reduce psychic influences from noises, excessive laboratory apparatus and the like Only one or two observers were present at any one time

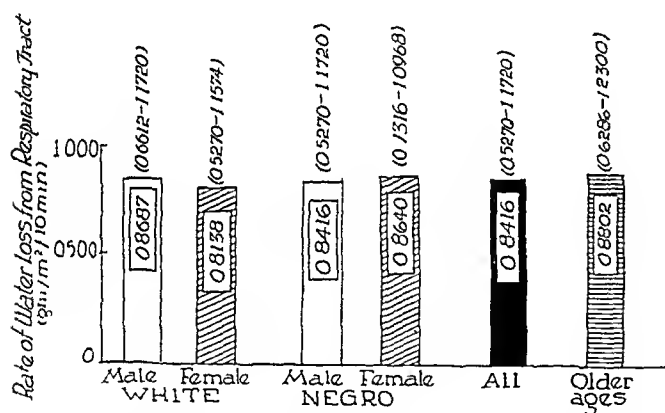


Fig 1—The rate of water loss from the respiratory tract of 56 normal young adults in a subtropical climate sitting in a comfortable environment (temperature 20.0 to 21.1 C and relative humidity 55 to 60 per cent) The older age group consists of 8 normal subjects varying from 50 to 60 years of age

After the rest period, the subject was connected to the apparatus During a period of five minutes the water and heat loss were measured A sling psychrometer was used from one to three times during the five minute period to determine the conditions of the room air At the completion of the five minute period the subject was allowed to rest for about ten minutes, and then the rate of his total body heat production, elimination of carbon dioxide, volume of tidal air and respiratory rate were recorded with a clinical type of Benedict-Roth BMR machine For many subjects

<sup>6</sup> Henceforth, a comfortable room will mean one with the air temperature and relative humidity as indicated

the measurements were repeated at intervals varying from a few minutes to days or weeks

For the sake of clarity and continuity of thought the various experiments and results are grouped separately for presentation and comment

## I THE RATE OF WATER LOSS FROM THE RESPIRATORY TRACT

During two hot summer months (August and September 1944) in New Orleans the mean rate of water loss from the respiratory tract for an entire group of 56 normal young adults varying in age from 17 to 43 years was 0.842 Gm per square meter of surface area of the body per ten minutes,<sup>7</sup> the extremes being 0.527 and 1.172 Gm The detailed values for the sexes and for the two races are shown in figure 1 There was

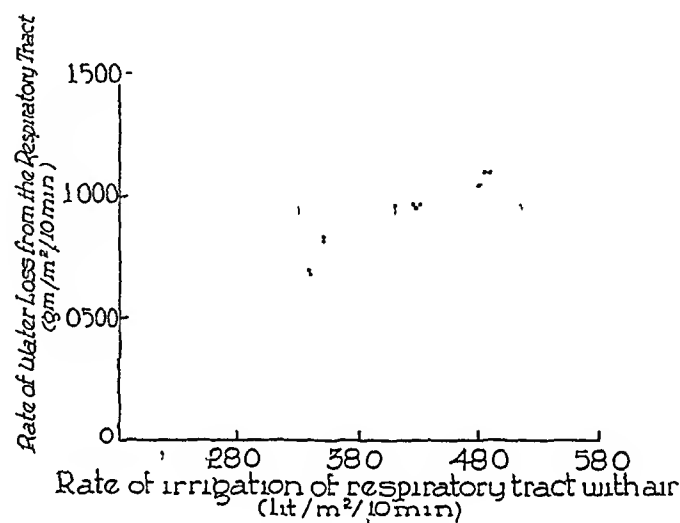


Fig 2—A representation of the high correlation of the rate of water loss from the respiratory tract and the rate of irrigation of the respiratory tract with air in 56 normal young adults sitting in a comfortable environment (temperature 20.0 to 21.1 C and relative humidity 50 to 60 per cent)

no significant difference due to sex or race The statistical constants for the rate of water loss were

Mean,  $0.878 \pm 0.030$  Gm per square meter per ten minutes

Standard deviation,  $0.333 \pm 0.021$  Gm per square meter per ten minutes

Coefficient of variation,  $37.90 \pm 2.49$  per cent

The mean rate with which the respiratory tract was irrigated with room air was 38.326 liters per square meter of surface area per ten minutes, the extremes being 28.316 and 53.250 liters There was no significant difference due to sex or race The statistical constants for the rate with which

<sup>7</sup> The rate of water loss is expressed henceforth in grams per square meter of surface area of the body per ten minutes All values, when indicated, were expressed according to surface area and ten minute intervals of time

the respiratory tract was irrigated with air were

Mean,  $38\,286 \pm 0\,933$  liters per square meter per ten minutes

Standard deviation,  $10\,216 \pm 0\,651$  liters per square meter per ten minutes

Coefficient of variation,  $26\,68 \pm 1\,82$  per cent

The individual values for the rate of water loss and the rate of irrigation of the respiratory tract with room air are shown in figure 2. There is a high positive correlation between these two variables. This is borne out by statistical analysis, the correlation coefficient being  $+0\,914 \pm 0\,015$ .

*The Influence of Season*—During the relatively cool month of January these observations were repeated on 27 normal young adults (8 were the same subjects studied during the summer and 19 were different) to study seasonal influences. The conditions of the experiments were the same as for the summer. There were no significant seasonal differences noted. The mean rate of water loss from the respiratory tract was  $0\,804$  Gm per square meter per ten minutes, with the extremes being  $0\,508$  and  $1\,205$  Gm. The mean rate of irrigation of the respiratory tract with air was  $35\,577$  liters per square meter per ten minutes, the extremes being  $26\,733$  and  $49\,211$  liters. The rate of water loss and irrigation of the respiratory tract with air correlated very highly again, the correlation coefficient being  $+0\,878 \pm 0\,030$ . Thus it can be seen that there was no significant seasonal influence on the rate of water loss from the respiratory tract.

*The Influence of Exercise*—The influence of mild exercise on water loss from the respiratory tract was studied in 5 normal young adults. In each subject the rate of water loss was measured as previously described, and then each was made to run in place with moderate rapidity for a period of ninety seconds, and the measurements were repeated. The effects of mild exercise on the rate of water loss, rate of irrigation of the respiratory tract with air and temperature of the expired air are summarized briefly by figure 3. The temperature of the expired air was not changed or was only slightly reduced by exercise, there being an average drop of only  $0\,3$  degree (C). The rate of water loss from the respiratory tract was definitely increased by exercise, an increase of  $36\,3$  per cent being recorded. The rate of irrigation of the respiratory tract with air likewise was increased, an increase of  $45\,1$  per cent being noted. The increase in the rate of water loss is to be expected, since exercise is known to increase the rate of irrigation of the lungs with air and as just noted, there is a

direct and high correlation of the rate of water loss from the respiratory tract with the rate of irrigation of the respiratory tract with air.

*The Influence of Breathing Through the Nose or Mouth on the Rate of Water Loss*—In the method employed the subjects breathed through the mouth. Normally most breathing is through the nose. To learn whether or not breathing through the nose or mouth would influence the results, measurements were made for five subjects, under identical conditions, breathing through the nose and then through the mouth. Special nose pieces were used for the nose. No significant difference was noted in the rate of water loss. For example, for 1 subject the rate of water loss through the nose was  $0\,6945$  Gm per square meter per ten minutes and through the mouth  $0\,6903$  Gm per square meter per ten minutes. The temperature of the expired air was essentially the same with both routes of breath-

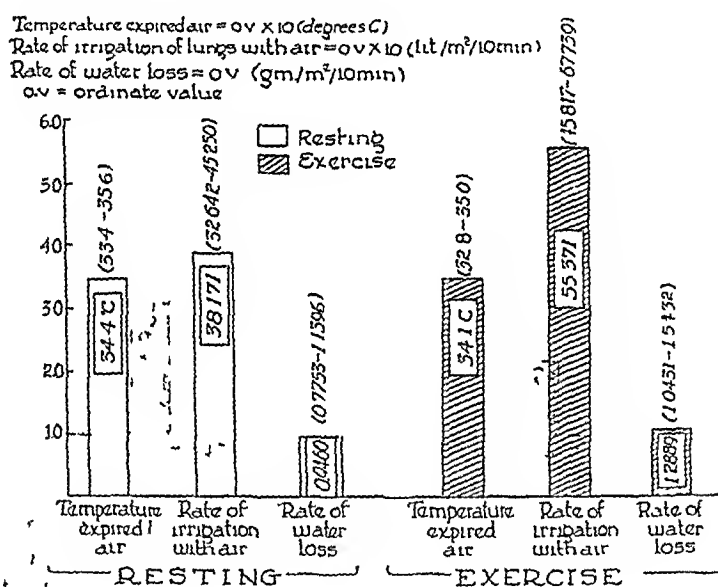


Fig 3—The effects of mild exercise on temperature of the expired air, rate of water loss and rate of irrigation of the respiratory tract with air in 5 normal young adults.

ing, averaging  $33\,6$  C for the nasal route and  $34\,4$  C for the oral route. There was complete overlapping of the variations. This conclusion is not surprising in view of the results of Seeley<sup>3</sup> and Christie and Loomis<sup>4</sup>. These observers showed that the greatest amounts of water and heat are added to inspired air in the alveoli, in which there is more surface area and, therefore more water and more heat in direct contact with the air. Whether or not the same results would be encountered in long experiments is not known. These studies lasted only five minutes.

*The Influence of Depth and Rate of Respiration on the Rate of Water Loss*—Seven normal subjects were studied under identical conditions for the rate of water loss from the respiratory tract with normal rapid and shallow breathing and

then with slow and deep breathing. No attempt was made to quantitate the rates or depths of breathing except to make certain that they were different.

The results are shown in figure 4. The rate of water loss from the respiratory tract essentially doubled with rapid and shallow breathing over that with normal quiet breathing and increased about 1.8 times with slow and deep breathing. There was a more or less comparable increase in the rate of irrigation of the respiratory tract with air. The quantity of air irrigating the respiratory tract and not the nature of the breathing was the principal factor which determined the rate of water loss. However, the data

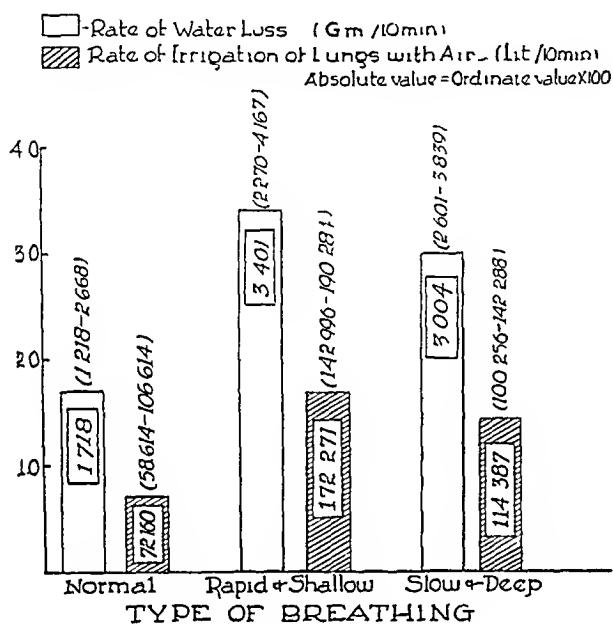


Fig 4—The influence of respiratory rate and depth on the rate of water loss. Again, the rate of water loss is determined mainly by the rate of irrigation of the respiratory tract by air.

(fig 4) show that more water is lost from the lungs per unit volume of air inspired with deep and slow breathing than with rapid and shallow. This greater water loss is probably due to the fact that the air remains in the lungs for a longer time with deep breathing, thus allowing more time for the water on the surface of the respiratory tract to evaporate and to diffuse into the inspired air before it is expired.

*The Effect of Room Temperature and Humidity (Cool and Dry, Cool and Foggy, Comfortable, Hot and Dry and Hot and Wet) on Water Loss*—Fourteen normal white adults (23 to 40 years old and all except 1 being female) were studied to learn the influence of variations in the room air on the heat and water loss from the respiratory tract. Some of the measurements were made on different days, since it was not possible to study the influence of all room conditions in immediate succession.

The results, including the absolute values, are summarized in figure 5 for rate of water loss, rate of irrigation of the lungs with air and the temperature and relative humidity of the expired air. The room conditions are indicated by the figure. The temperature of the expired air, the relative humidity of the expired air, the rate of water loss from the respiratory tract and the rate of irrigation of the respiratory tract with air were not significantly different when the subjects were breathing air in a cool dry room, a cool foggy room or a comfortable room (fig 5). When the room temperature was increased to about 50 C, the rate of water loss did not change significantly, but there was a significant increase in the temperature of the expired air and in the rate of irrigation of the lungs with air. The temperature of the inspired air (room air) was increased over that for the comfortable room conditions by about 30 C, while the temperature of the expired air increased only about 6 degrees (C). This difference indicated a significant absorption of heat by the respiratory tract, with a cooling of the inspired air by the respiratory tract by about 10 C.

In the hot humid atmosphere there was a decided drop in the rate of water loss from the respiratory tract and a definite drop in the relative humidity of the expired air, while the temperature of the expired air and the rate of irrigation of the respiratory tract increased slightly over that in a hot and dry atmosphere. It is obvious that in a hot and humid atmosphere the rate of water loss does not obey the same laws governing the relation with the rate of irrigation of the respiratory tract with air.

These findings deserve special comment. That the rate of water loss from the respiratory tract is not significantly different when an atmosphere of cool dry, cool foggy or a comfortable air is breathed is to be expected, since the absolute quantities of water vapor per unit volume of air at 15 C and 60 per cent relative humidity, 15 C and 94 per cent relative humidity or 20 C and 52 per cent relative humidity are not very different, the values being 7.9, 12.4 and 12.7 mg per liter, respectively.<sup>8</sup> When it is remembered that expired air has a temperature of about 33 C and a relative humidity of about 88 per cent and therefore contains 31.6 mg per liter, it can be seen that large and essentially equal amounts of water can be and are added to the inspired air under the three room conditions before it is expired.

<sup>8</sup> Marvin, C. F. Psychrometric Tables, United States Department of Agriculture, Weather Bureau, 1915.

When hot (much above body temperature) air is inspired, the problem becomes different. For example, when hot dry air, 50 C and 18 per cent relative humidity, containing 13.3 mg per liter, is inspired and merely cooled by the respiratory tract to about 39 C, as has been indicated, the relative humidity of the inspired air suddenly increases to about 38 per cent, still containing 13.3 mg per liter. This air is capable of taking on more water than cool air, but its dryness and its ability to remove water from the respiratory passage are not as great as might be expected at a first glance, that is, when erroneously considering the hot dry air inspired without the effects of

pure. Furthermore, the vapor pressure of air at 39 C and 80 per cent relative humidity is extremely high, and the water vapor would therefore be forced out of the nose or mouth into the atmosphere with much lower vapor pressures before high values of relative humidity could be reached. In a hot and humid environment, then, the rate of water loss from the respiratory tract would be expected to decrease, while in a cool and foggy air (relative humidity high and absolute amount of water relatively low) the rate of water loss would not be expected to be significantly different from that in a comfortable environment.

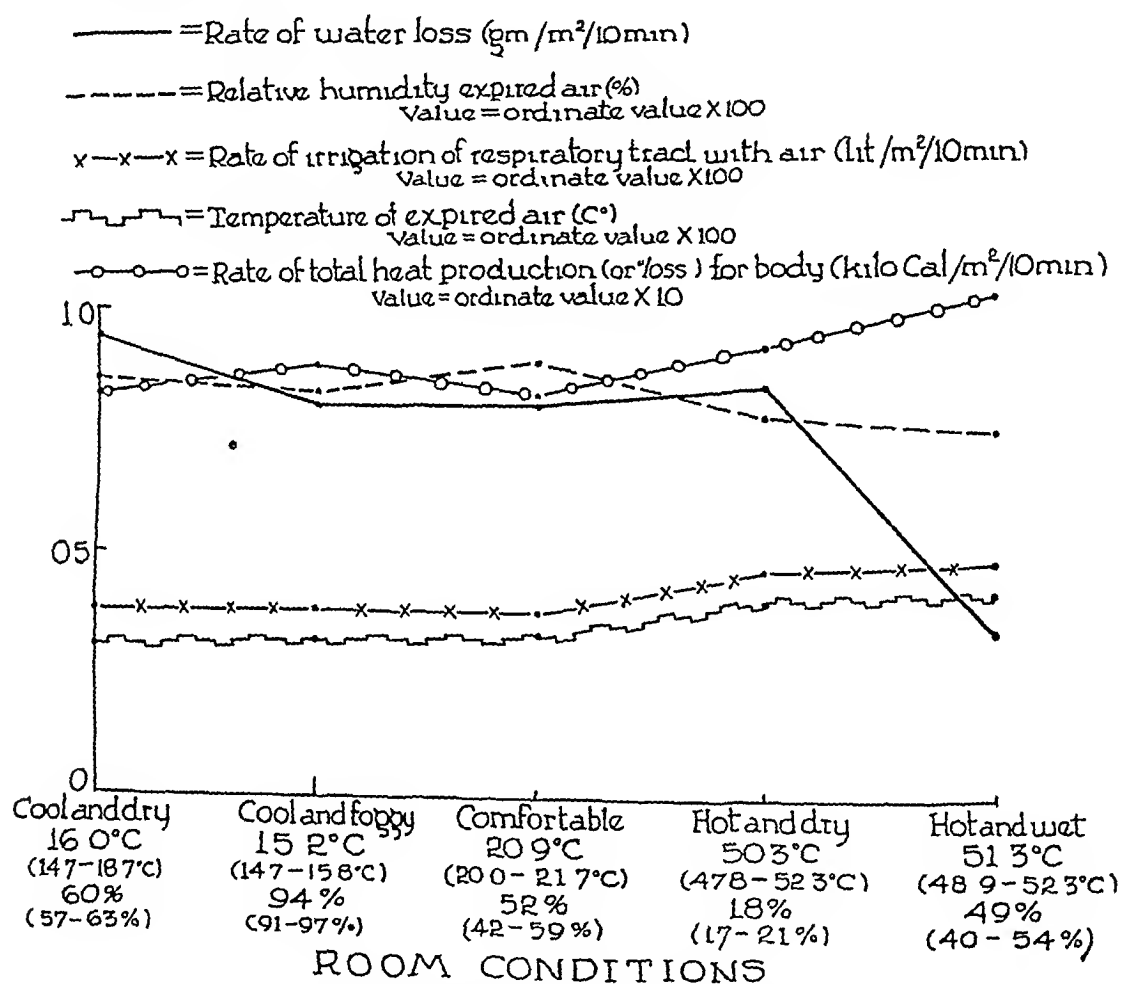


Fig 5—A graphic representation of the influence of room temperature and humidity on rate of water loss, temperature of expired air, rate of irrigation of lung with air, relative humidity of the expired air and total heat production

cooling by the respiratory tract. This effect of cooling on hot humid air (50 C and 49 per cent relative humidity) is even more pronounced. When such air, containing 37.1 mg of water per liter, is merely cooled by the respiratory passage to 39 C, its relative humidity is raised to 80 per cent, but it still contains the same 37.1 mg of water per liter of air, so that little water can be added to this air by the respiratory tract. This phenomenon was verified and is indicated in figure 5. Again it is impossible to reach a 100 per cent relative humidity in expired air, because the water on the surface of the membranes of the respiratory tract is not chemically

## II TEMPERATURE OF EXPIRED AIR

The temperature of the expired air measured with a thermocouple in 27 sitting normal young adults was found to vary between 31.6 and 34.2 C when the air inspired had a mean temperature of 20.5 C (extremes 19.5 and 21.4 C) and a mean relative humidity of 57.2 per cent (extremes 54 and 61 per cent). The statistical constants found were

Mean,  $33.19 \pm 0.21$  C

Standard deviation,  $1.58 \pm 0.15$  C

Coefficient of variations,  $4.76 \pm 0.44$  per cent

As reported previously,<sup>5</sup> the temperature of the expired air did not vary significantly with

the temperature of the inspired air when it was as low as 20 C and as high as 36 C. When air temperatures higher than 36 C were inspired, the temperature of the expired air increased.<sup>5</sup> Weyrich<sup>1d</sup> found the temperature of the expired air to change little even when the temperature of the inspired air was as low as 0 C. The temperature of the expired air reported in the literature varies a great deal in some instances, but most of the reports<sup>9</sup> agreed with the values found in these studies.

When the subjects inspired air from a cool dry atmosphere, the mean temperature of the expired air was 33.1 C, the extremes being 31.7 and 34.2 C. When they inspired cool foggy air, the mean temperature of the expired air was 32.9 C (extremes 32.2 and 33.6). When hot dry or hot moist air was inspired the mean temperature of the expired air was 39.6 C (extremes 38.1 and 40.6 C) and 42.1 C (extremes 40.6 and 43.4 C) respectively.

### III RELATIVE HUMIDITY OF EXPIRED AIR

The temperature and the total quantity of water in the expired air were determined<sup>8</sup> and the relative humidity calculated. A statistical analysis of the data collected in a study of 27 normal young sitting adults breathing room air at 20.5 C (range 19.5 to 21.4 C) with a relative humidity of 57.2 per cent (range 54 to 61 per cent) resulted in the following constants:

Mean,  $88.15 \pm 1.31$  per cent

Range, 78 to 96 per cent

Standard deviation,  $9.87 \pm 0.92$  per cent

Coefficient of variation,  $11.20 \pm 1.06$  per cent

Three values of relative humidity were relatively high, they were 95.0, 95.8 and 96.5 per cent. These were high when compared with the other values. Since such high values were not found when the determinations were repeated, they therefore may have been in error.

A mean value of 88 per cent for the relative humidity of the expired air is consistent with the known physical and physiologic facts. It is physically impossible to obtain a 100 per cent relative humidity in expired air, since the water on the surfaces of the respiratory tract is not chemically pure. Claims of finding complete saturation of expired air with water have been made by many observers.<sup>10</sup> These claims are invalid because of obvious errors.

<sup>9</sup> Weyrich<sup>1d</sup> Galeotti<sup>1g</sup> Seeley<sup>3</sup>

<sup>10</sup> (a) Osborne, W. A. *Water in Expired Air*, J. Physiol. **47** 12, 1913. (b) Luciani, L. *Human Physiology*, New York, The Macmillan Company, 1913, vol. 1, p. 397. (c) Lefevre, cited by Hill, L. *The Science of Ventilation and Open Air Treatment*, London, His Majesty's Stationery Office, 1919. Weyrich<sup>1d</sup>

The relative humidity of the expired air is influenced by the temperature and relative humidity of the inspired air. This fact has been commented on and is illustrated by figure 5. When cool dry or cool foggy air was inspired, the mean relative humidity of the expired air was 86.1 per cent (extremes 83 and 94 per cent) or 83 per cent (extremes 79 and 91 per cent, respectively). When hot dry and hot moist air was inspired, the mean relative humidity of the expired air was 75.8 per cent (extremes 60 and 91 per cent) or 74.4 per cent (extremes 71 and 83 per cent, respectively).

### IV WATER LOSS AND METABOLIC RATE

For the 27 normal young resting adults a correlation coefficient of  $-0.26$  was found between water loss from the respiratory tract and the rate of metabolism at that moment. Since metabolic rate is really a measurement of oxygen consumption while water loss is not necessarily dependent on oxygen consumption but (under comfortable environmental conditions) on the rate of irrigation of the respiratory tract with air, a correlation coefficient such as  $-0.26$  might be expected. This means that more air circulated through the lungs than was necessary to meet the demands for oxygen. In normal subjects only the necessary amount of oxygen is removed from the air inspired. Emotional unrest, for example, might increase the rate of respiration beyond that necessary for the metabolic requirements. It is possible that such a factor was active in these studies.

That more air circulated through the lungs than was necessary for metabolic or oxygen needs is evidenced by the fact that a correlation coefficient of only  $+0.07$  was found when the metabolic rate was correlated with the rate of irrigation of the respiratory tract with air. It must be remembered that the subjects studied were not in a basal metabolic state.

### V HEAT LOSS FROM THE RESPIRATORY TRACT

In 27 normal young white resting adults (ages varying from 17 to 36, mean 24 years) the heat loss from the respiratory tract was measured as outlined in a previous paper.<sup>5</sup> The room air, or inspired air, had a mean temperature of 20.5 C (range 19.5 and 21.4 C) and a mean relative humidity of 57.2 per cent (range 54 and 61 per cent). The heat loss was measured for the three components simultaneously (fig. 6): (1) heat loss by the evaporation of water,  $h_F$ , (2) heat loss by convection (warming of inspired air),  $h_c$ , and (3) heat loss by decomposition of carbonic acid and expiration of carbon dioxide.

gas,  $h_{CO_2}$ . The total heat loss from the respiratory tract,  $H$ , was determined by the summation of these three components

The total heat loss from the body was estimated by means of a Benedict-Roth type of BMR machine.<sup>11</sup> Since the subjects had been resting in the observation room for over thirty minutes, it was assumed that there was thermal equilibrium between the subject's body and the environment. From this value for total body heat loss it was then possible to express heat loss from the respiratory tract (total or any of the three components) as per cent of total heat loss from the entire body.

1 *The Rate of Heat Loss by the Evaporation of Water ( $h_E$ )*—The heat loss by the evaporation of water varied between 0.305 and 0.706

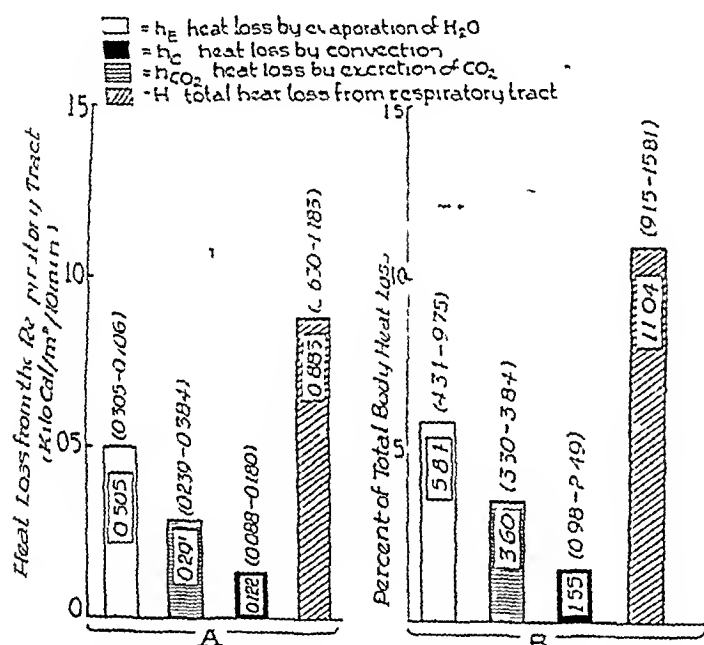


Fig 6—The rate of heat loss from the respiratory tract, showing its various components

kilogram calories per square meter per ten minutes.<sup>11</sup> The statistical constants found were

Mean,  $0.505 \pm 0.017$  kilogram calories per square meter per ten minutes

Standard deviation,  $0.191 \pm 0.012$  kilogram calories per square meter per ten minutes

Coefficient of variations,  $37.90 \pm 2.49$  per cent

The relative importance of  $h_E$  in total pulmonary heat loss is shown in figure 6

The mean rate of heat loss for the entire body was found to be 8.10 (extremes 6.62 and 10.77) kilogram calories. The heat loss from the respiratory tract by evaporation ( $h_E$ ) represented a mean of 5.84 per cent of the total body heat loss (extremes 4.34 and 9.75 per cent). As an

<sup>11</sup> All values for heat loss are expressed in kilogram calories per square meter of surface area of the body per ten minutes. This unit will not be repeated, only the numerical values will be indicated.

average, the  $h_E$  represented 53.2 per cent of  $H$  (total heat loss from the lungs)

Heat loss by evaporation varied with variations in environmental temperature and relative humidity (fig 7). There were no significant variations in  $h_E$  when the atmosphere was changed from a cool dry to a cool wet and then to a comfortable environment. In a hot dry environment,  $h_E$  remained unchanged, but when the environment was hot and moist  $h_E$  decreased significantly (fig 7). These changes are the result of the influences of these environmental conditions on the evaporation of water from the respiratory tract. Therefore, in a hot and humid environment heat loss by evaporation of water from the respiratory tract becomes much less significant, accounting for about 6 per cent of total heat loss in cool or comfortable environments. In a hot atmosphere saturated with water  $h_E$  would be 0.

Because of the high correlation between rate of water loss and rate of irrigation of the respiratory tract with air, the same high type of correlation would hold for  $h_E$  and rate of irrigation of the respiratory tract with air. In fact, the value of the correlation coefficient would be the same.

The importance of  $h_E$ , as in thermal equilibrium, depends on the conditions of the environment, especially in a subtropical and tropical climate.

2 *The Rate of Heat Loss by Warming Inspired Air (Convection,  $h_C$ )*—The heat loss by the warming of inspired air in 27 normal young adults sitting in a comfortable environment (temperature 21°C and humidity 52 per cent) is shown graphically in figure 6. The relative importance of this factor in total pulmonary heat loss is indicated by figure 6. The statistical constants found for  $h_C$  were

Mean,  $0.122 \pm 0.004$  kilogram calories per square meter per ten minutes

Range, 0.088 and 0.180 kilogram calories per square meter per ten minutes

Standard deviation,  $0.029 \pm 0.003$  kilogram calories per square meter per ten minutes

Coefficient of variation,  $23.77 \pm 2.31$  per cent

It can be seen that  $h_C$  averaged about 13.9 per cent of the total heat loss from the lungs ( $H$ ) and averaged 1.55 per cent of the total body heat loss under the comfortable environmental conditions.

When the temperature and the relative humidity of the room air were changed, the value for  $h_C$  varied (fig 7). There were relatively little or insignificant differences in  $h_C$  in cool dry, cool foggy or comfortable environments. This lack of difference is due to

the compensating influence of the rate of irrigation of the respiratory tract with air. The value of  $h_c$  would tend to be higher when cool air was inspired, but when cool air was inspired the amount of air inspired per unit of time was less than in the comfortable atmosphere. There was a definite change in  $h_c$  when the room air was raised above body temperature (fig 7). Instead of losing heat by convection, the body gained heat from the atmosphere,  $h_c$  becoming a positive value. Heat loss by convection was affected relatively little by the moisture in the air other than through its effect on the density and specific heat of the expired air.

At constant atmospheric conditions, because of the nature of the calculation of  $h_c$ ,<sup>5</sup> a high correlation between  $h_c$  and rate of irrigation of the respiratory tract with air would naturally

Standard deviation,  $0.065 \pm 0.006$  kilogram calories per square meter per ten minutes

Coefficient of variation,  $22.34 \pm 2.15$  per cent

Figure 6 shows the relative significance of  $h_{CO_2}$  when compared with other factors concerned with pulmonary loss of heat. The mean loss of heat by  $h_{CO_2}$  was 33.0 per cent of the total heat loss from the respiratory tract and averaged 3.60 per cent of the total body heat loss.

The value of  $h_{CO_2}$  is not influenced a great deal by the condition of the atmosphere (fig 7) other than those concerned with changes in the rate of irrigation of the respiratory tract with air ("washing" out of carbon dioxide from the blood) and changes in the metabolic rate. In a hot and humid environment the metabolic rate and rate of irrigation of the respiratory tract

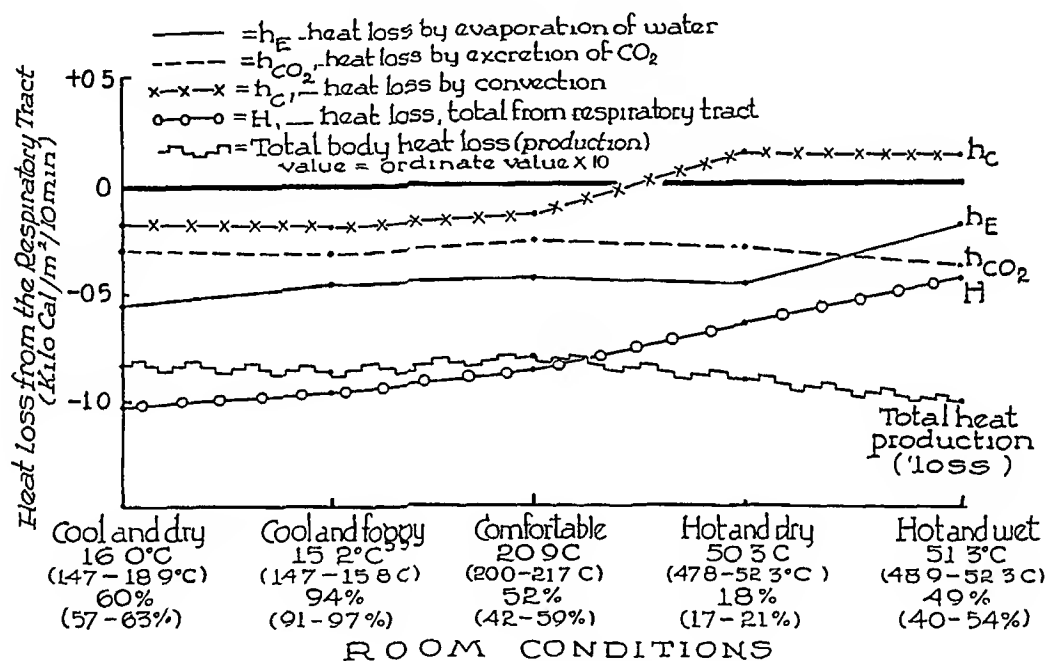


Fig 7—The mean rate of heat loss for various room conditions in 27 normal young adults. The total heat loss for the entire body, measured with a Benedict-Roth BMR apparatus, was considered to represent the total heat loss from the body, since the body was in thermal equilibrium with the environment. In the hot room there is probably storage of heat, and therefore this assumption does not apply, particularly not to the hot and humid room. The relative loss of heat by the various components and their correlations are evident.

follow. Although  $h_c$  is not large, it can become important under certain conditions of low or high atmospheric temperatures (for example, subtropical and tropical climates).

3 *The Rate of Heat Loss by the Excretion of Carbon Dioxide ( $h_{CO_2}$ )*—Simultaneously with the measurement of the foregoing two types of heat loss in the 27 normal subjects sitting in a comfortable environment, the heat loss by the expiration of carbon dioxide was measured. The statistical constants found for  $h_{CO_2}$  are

Mean,  $0.291 \pm 0.008$  kilogram calories per square meter per ten minutes

Range, 0.239 to 0.384 kilogram calories per square meter per ten minutes

with air are increased (fig 5). These were found to be associated with an expected increase in  $h_{CO_2}$ .

Judging by the nature of the method for measuring  $h_{CO_2}$ , a high correlation of  $h_{CO_2}$  with the metabolic rate would be expected.<sup>5</sup> The importance of  $h_{CO_2}$  in thermal equilibrium in man in a tropical and subtropical climate, though relatively small, is self evident from these comments.

4 *The Rate of Total Heat Loss from the Respiratory Tract ( $H$ )*—The total heat loss from the respiratory tract is

$$H = h_F + h_c + h_{CO_2}$$

The relative values of  $H$  and its three components are shown in figure 6

In the study of the 27 normal young adults sitting in a comfortable atmosphere,  $H$  was found to have the following statistical constants

Mean,  $0.886 \pm 0.034$  kilogram calories per square meter per ten minutes

Range, 0.630 to 1.183 kilogram calories per square meter per ten minutes

Standard deviation,  $0.264 \pm 0.024$  kilogram calories per square meter per ten minutes

Coefficient of variation,  $29.80 \pm 2.98$  per cent

The total heat loss from the respiratory tract ( $H$ ) averaged 11.04 per cent of the total body heat loss, the extremes being 9.15 and 15.181

The total heat loss from the respiratory tract varied with the temperature and humidity of the environment (fig 7). In a cool environment with a low or high relative humidity,  $H$  changed relatively little. In a hot environment with the temperature greater than body temperature,  $H$  decreased significantly. This decrease was especially great in a hot and humid atmosphere (fig 7).

Although the rate of total heat loss from the respiratory tract decreased in the hot and humid environment, the rate of heat production increased noticeably. The decrease in  $H$  in the hot and humid atmosphere is due mainly to the decrease in  $h_r$  and the change in  $h_c$ . Under those atmospheric conditions  $h_c$  becomes a positive rather than a negative value. Instead of body heat being lost by convection, it is being increased by this factor. The significance of these phenomena in thermal regulation in a tropical and subtropical climate is evident from figure 7.

#### VI THE RATE OF PRODUCTION AND LOSS OF TOTAL BODY HEAT

The rate of total heat production for the body as a whole was measured with a Benedict-Roth BMR machine for the 27 normal young adults sitting quietly in a comfortable environment. Since the environment was comfortable and the subjects had rested for a period of thirty minutes or more prior to the measurements, the subjects were considered to be in thermal equilibrium with their environment and therefore the rate of heat production and heat loss were considered equal. The statistical constants found for total heat loss from the body are

Mean,  $8.08 \pm 0.19$  kilogram calories per square meter per ten minutes

Range, 6.62 to 10.77 kilogram calories per square meter per ten minutes

Standard deviation,  $1.50 \pm 0.14$  kilogram calories per square meter per ten minutes

Coefficient of variation  $18.51 \pm 1.75$  per cent

In a hot and dry environment the rate of total body heat production increased. When the humidity of the hot atmosphere was further increased, the rate of total body heat production also increased (fig 7). When the temperature of the atmosphere was greater than that of the body ( $50^\circ\text{C}$ ), thermal equilibrium between the subject and his surroundings did not occur, and therefore the rate of heat production was not equal to heat loss. The exact nature of the state of transfer of heat between the subject as a whole and the environment was not known during these studies, especially when the room air was hot. In spite of this, the rate of total body heat production was intentionally, although erroneously, considered equal to the rate of total loss of body heat to make it possible to obtain an idea of the part played by the respiratory tract in the elimination of body heat at the high room temperatures.

#### VII STUDIES OF THE RATE OF WATER AND HEAT LOSS FROM THE RESPIRATORY TRACT OF ONE SUBJECT

One subject, a young (34 years of age) white man sitting quietly, was studied at frequent intervals for seven consecutive hours during one day (beginning at 10 a.m.). The rate of water loss, rate of heat loss from the respiratory tract (the three components and total), rate of total heat loss from the entire body, temperature of the expired air, rate of irrigation of the respiratory tract with air and relative humidity of the expired air were among the factors recorded (fig 8). The room conditions are indicated by figure 8. The physiologic phenomena recorded were remarkably constant, the main change occurring shortly after a moderately heavy noon meal (fig 8).

The same subject was similarly studied several times over a period of months, extending from the hot summer month of August to the cool month of January. The results are summarized for the rate of water loss in figure 9. The conditions of the room were the same, being comfortable and having values as indicated for that type of room in figure 8. There were no significant differences from month to month as the season changed from summer to winter in New Orleans. There were fluctuations from month to month, but they were considered to be ordinary physiologic variations.

#### COMMENT

It is apparent that the expired air is not saturated with water and could not possibly be so. As found in these studies, it is only about 88 per cent saturated when the subject is breathing air.

in a comfortable environment as well as when he is breathing cool dry or foggy air. This conclusion is in keeping with the recent studies of Seeley<sup>3</sup> and Christie and Loomis<sup>4</sup>. It was also found many years ago by Loewy and Gerhartz<sup>11</sup>. It is well to note that Galeotti<sup>12</sup> found the expired air to be 78 per cent saturated at 37 C and completely saturated at a temperature of 32.5 C. The temperatures of the expired air were assumed in his studies, thus rendering his statements of relative humidity of expired air of only academic interest. Galeotti<sup>12</sup> at a later date measured the temperature of the expired air with a thermocouple and found it to vary between 34.4 and 35.7 C. Liljestrand and Sahlstedt<sup>12</sup> found the expired air to have a 98 per cent satu-

tion that expired air is saturated at 37 C. As was shown, the expired air is neither saturated nor at 37 C when subjects are in a comfortable atmosphere.

The majority of observers<sup>14</sup> found the temperature of the expired air to be about 32 to 33 C. The values observed in these studies are in keeping with these figures rather than with some of the higher values for a comfortable atmosphere. The mean temperature of the expired air with the subject resting quietly was found to be 33.2 C, with extremes of 31.6 and 34.2 C.

When the temperature and the relative humidity of the atmosphere are changed the nature of the expired air changes. The tempera-

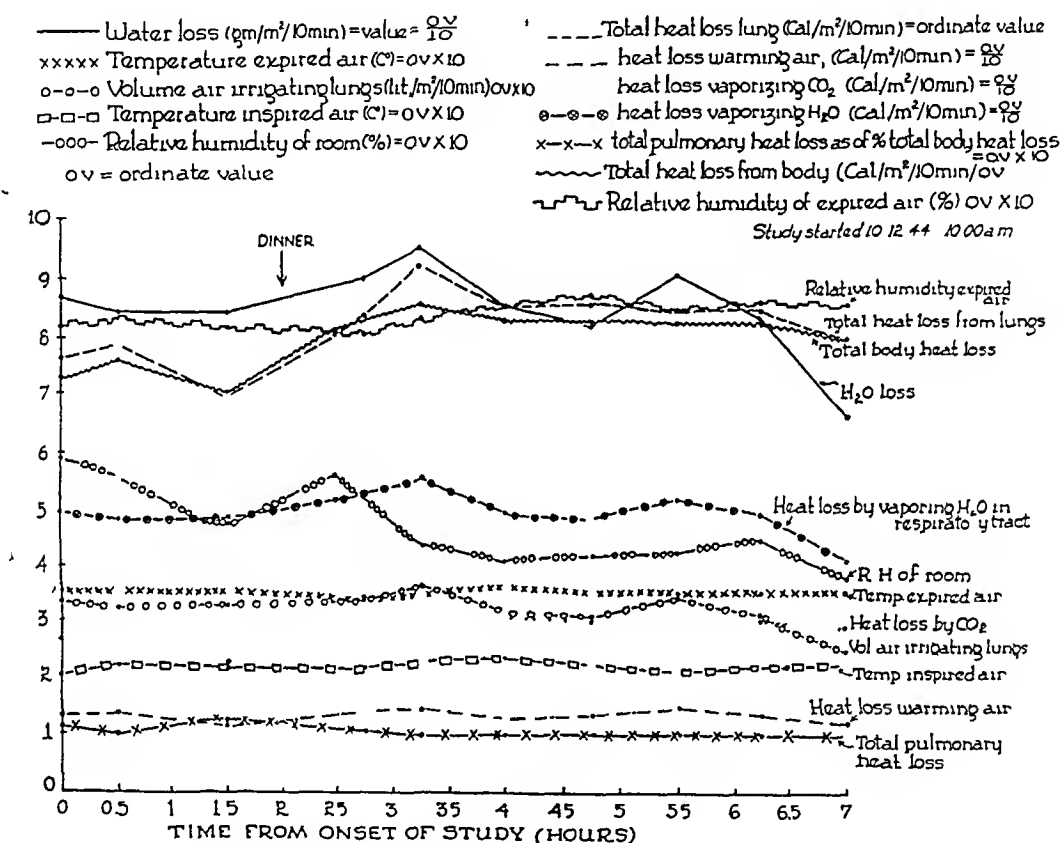


Fig 8—A study of the rates of water loss and heat loss from the respiratory tract of a normal young man made over a seven hour period (beginning at 10 a.m.) All factors noted were recorded at frequent intervals, that is, at the times indicated by the abscissa.

ation at a temperature of 30 to 35 C. The statements of Weyrich,<sup>12</sup> Luciani,<sup>10b</sup> Lefevre<sup>10c</sup> and Osborne<sup>10a</sup> that expired air is saturated with water were erroneous. Benedict and Carpenter<sup>13</sup> employed the method of Zuntz to calculate water loss from the lungs. These calculations are in error, since they were based on the assump-

ture and relative humidity of the expired air does not change significantly when the atmospheric conditions are made cool and dry or cool and wet. As just mentioned, cool air, whether wet or dry, shows little difference in the absolute amount (grams) of water vapor per unit volume, although the relative humidity may vary considerably. When the atmospheric temperature is elevated considerably, the capacity of the air to hold water is increased considerably, so that relatively small differences in relative humidity mean great differ-

12 Liljestrand, G, and Sahlstedt, A. V. Temperatur und Feuchtigkeit der Ausatemmeter Luft, Skandinav Arch f Physiol 46 94, 1924

13 Benedict, F. G, and Carpenter, T. M. The Metabolism and Energy Transformations of Healthy Man During Rest, Washington, D. C., Carnegie Institution of Washington, 1910

14 Galeotti<sup>12</sup> Galeotti<sup>12g</sup> Loewy and Gerhartz<sup>11</sup> Seeley<sup>3</sup> Loewy and Gerhartz<sup>11b</sup>

ences in absolute humidity. These great influences of relative humidity of hot air on the rate of water loss (and also heat loss by evaporation of water) from the respiratory tract were shown by these observations. At a room temperature of 50 C and at 18 per cent relative humidity, the rate of water loss (heat loss by evaporation also) from the respiratory tract is increased over that at conditions in a comfortable environment. In an atmosphere of 50 C and 49 per cent relative humidity, the rate of water loss is noticeably decreased. The same is not true for a cool atmosphere. The rate of water loss for an atmospheric temperature of 15 or 16 C, whether 60 or 97 per cent saturated, was essentially the same. It is apparent that expressions of the moisture content of the atmosphere in vapor pressure or absolute humidity rather than relative humidity would give a much clearer concept of the physical factors concerned with water loss from the respiratory tract.

It is interesting to note that the surface area of the respiratory tract has been estimated to be

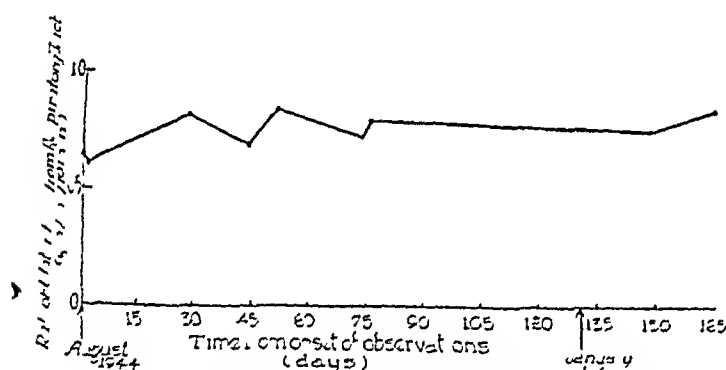


Fig 9—The rate of water loss from the respiratory tract over a period of several months in a normal young man sitting in a comfortable environment (temperature  $20.9 \pm 0.9$  C)

about 70 square meters during quiet breathing and 90 square meters when moderately inflated. That of the alveoli alone is about 55 square meters.<sup>15</sup> Some estimates as high as 129 square meters have been made. Pulmonary area over thirty times that of the external (skin) area of the body is truly large and therefore an important factor concerned with water and heat loss from the respiratory tract.

The role of the respiratory tract in the maintenance of thermal equilibrium between heat produced in the body and that lost to the surrounding atmosphere is significant. In a normal adult sitting in a comfortable environment, the total heat loss from the respiratory tract accounts for about 11 per cent of the total heat loss from the body. This percentage is great enough to war-

rant serious consideration. The importance of this factor is even more evident when it is considered that the habits of man today render it impossible to vary this loss even under extreme conditions of environmental temperature. By the use of clothing it is possible to influence the amount of heat lost from the external, or cutaneous, surface of the body. In the case of the respiratory tract no such simple procedures for varying heat loss are available. In a cool or uncomfortably cold environment, the heat loss from the respiratory tract remains relatively unchanged except for the factor  $h_i$  (warming of cold inspired air). Considering the surface area of the respiratory tract and the influence of cold on blood vessels, glandular function and the like of the entire respiratory tract, it is indeed not surprising to note a great tendency for infections of the respiratory tract to develop in the cold months of the year. Among persons exposed to cold environments because of occupational military or other reasons for prolonged periods of time, the role of the respiratory tract in heat loss is important enough to demand more consideration than it usually commands.

In a hot and humid environment, when heat loss from the skin is definitely impaired, the heat loss from the respiratory tract likewise is impaired. The loss of heat by  $h_{CO_2}$  remains unchanged or may increase with the increase in excretion of carbon dioxide (Bazett<sup>16</sup>). When the temperature of the environment is greater than body temperature,  $h_e$  becomes a positive value, and heat is absorbed from the surrounding atmosphere. The high humidity reduces heat loss by the evaporation of water. Therefore the respiratory tract is of little value in the elimination of body heat in a hot and humid environment. As indicated previously, if the environmental temperature is sufficiently high, the relative humidity does not have to be very high in order to effect a much higher effective relative humidity. For when hot air (50 C) only about 50 per cent saturated becomes about 80 per cent saturated on being cooled to 39 C by the respiratory tract, the resulting high relative humidity of hot air after inspiration is considerably different from the relative humidity of the room air.

It is frequently stated that a subject inspiring foggy air will gain water from the atmosphere by a deposition of many small droplets of water on the surface of the epithelium of the respiratory tract. That this may be erroneous, unless large droplets of water form the fog, is indicated by

<sup>15</sup> Willson, H. G. The Terminals of the Human Bronchioles, *Am J Anat* 30:267, 1922.

<sup>16</sup> Bazett, H. C. Physiological Responses to Heat, *Physiol Rev* 7:531, 1927.

the aforementioned observations. When a subject inspires air at 15 C and 97 per cent relative humidity (cool foggy air), the temperature of the air is raised to about 33 C, and it is then no longer foggy, is far from saturated and is capable of readily taking on a great deal more water. It does remove water from the epithelium of the respiratory tract. Water is not absorbed from the atmosphere but is readily lost to it.

To fulfil the metabolic requirements, a certain amount of oxygen must be absorbed from the atmosphere and a certain amount of carbon dioxide excreted into it. The quantity of carbon dioxide excreted will be influenced less by the temperature and humidity of the air inspired than the water vaporized or heat lost by convection. Therefore, heat loss by excretion of carbon dioxide remains relatively constant in various atmospheric conditions, all other factors being constant.

The lack of correlation of the metabolic rate (oxygen consumption) and rate of irrigation of the respiratory tract with air indicates that the rate of circulation of air through the lungs is not governed only by the oxygen requirements. This physiologic fact is well known. The dog, for instance, increases the rate of breathing when in a hot environment. This increase may occur to some extent in man, whether or not this is concerned to any extent with cooling remains unknown.<sup>16</sup> However, as would be expected, there is a high positive correlation of rate of irrigation of the lungs with air and the rate of water loss from the lungs.

Boyer and Bailey<sup>17</sup> found a fair correlation ( $+0.58 \pm 0.02$ ) between surface area of the body and the ventilation of the lungs (liters per minute) and a high correlation between ventilation and heat production in normal subjects in the basal state. In the latter correlation, no corrections were made for body size. Such a correction, if made in units of surface area, would have reduced the value of the correlation coefficient of  $+0.90$  to something approaching  $+0.58$ . This factor explains in part the lack, in our studies, of a high correlation between the rate of irrigation of the lungs and metabolic rate. The differences in time of measurements of the metabolic rates and the rate of irrigation of the lungs, position of the subject and the subject's resting, but definitely not basal, state are among the factors which are responsible for differences between the findings reported here and those of Boyer and Bailey.<sup>17</sup>

<sup>17</sup> Boyer, P. K., and Bailey, C. V. Concentration of Carbon Dioxide in Expired Air, *Arch Int Med* 69:773 (May) 1942.

## SUMMARY AND CONCLUSIONS

The rates of water loss and heat loss from the respiratory tracts of 107 young normal resting (sitting) adults were studied. These subjects lived in a subtropical climate (New Orleans). They varied in age from 17 to 43 years and represented both sexes and the white and Negro races.

A comfortable environment of reference (temperature 20 to 21.1 C and relative humidity 55 to 60 per cent) was used in all groups of measurements.

For 56 young normal adults sitting in the comfortable room and studied during the hot month of August 1944, the mean rate of water loss from the respiratory tract was 0.878 Gm per square meter of surface area of the body per ten minutes, the extremes being 0.527 and 1.172 Gm. Twenty-seven similar subjects (some were in the group of 56) observed under similar conditions but studied during the cool month of January had a mean rate of water loss from the respiratory tract of 0.804 Gm per square meter per ten minutes, the extremes being 0.508 and 1.205 Gm. Thus no seasonal difference was noted. There were no differences due to sex or race.

The mean rate of irrigation of the lungs for the 56 young normal subjects was 38.326 liters per square meter per ten minutes, the range being 28.316 and 53.250 liters. There was an extremely high positive correlation between the rate of irrigation of the lungs and the rate of water loss from the respiratory tract, the coefficient of correlation being  $+0.914 \pm 0.015$ .

Exercise increased the rate of water loss from the respiratory tract essentially in proportion to the resultant increase in the rate of irrigation of the respiratory tract with air.

There was no significant difference between the results obtained for water loss whether the subject respired through the nose or mouth.

The depth and rate of respiration influenced the rate of water loss from the respiratory tract mainly on the basis of the rate of irrigation of the respiratory tract with air. Slow deep breathing was, however, associated with more water loss per unit of volume of air respired than was rapid shallow breathing. In the former type of breathing the air remained in the respiratory tract a longer time, thus permitting more water vapor to diffuse into the air inspired.

The rate of water loss from the lungs was changed little from that in a comfortable environment when the environmental temperature was cooled to about 15 C. At that temperature the relative humidity of the air, even saturated to the extent of producing fog, changed the rate of water

loss from the respiratory tract relatively little. Some of the mechanisms involved in the lack of differences were studied.

The rate of water loss was increased by a hot (50 C) and dry (18 per cent relative humidity) atmosphere. It was noticeably decreased when the hot (50 C) atmosphere was moistened (49 per cent saturated) but not nearly saturated. The mechanisms involved were studied.

The mean temperature of the expired air with the subjects resting in the comfortable atmosphere was  $33.18 \pm 0.21$  C. A drop in the environmental temperature to about 20 C did not influence the temperature of the expired air. An increase in the temperature of the atmosphere to about 35.5 C had no significant influence on the temperature of the expired air. When the temperature of the atmosphere was increased above 35.5 C, there was a definite rise in the temperature of the air expired.

The mean relative humidity of expired air was found to be  $88.15 \pm 1.31$  per cent, the extremes being 78 and 96.5 per cent. The relative humidity of the air expired varied with that of the air inspired, especially if the inspired air was hot. Hot and relatively dry atmospheric air reduced the degree of saturation of expired air.

There was no significant correlation between the rate of water loss and the metabolic rate. This lack of correlation was to be expected, since the irrigation of the lungs is not determined by oxygen requirements only.

The rates of total heat loss from the respiratory tract and of its three components were determined simultaneously. Heat is lost from the respiratory tract by evaporation of water ( $h_E$ ). In 27 normal young adults sitting in a comfortable environment the mean value for  $h_E$  was  $0.505 \pm 0.017$  kilogram calories per square meter per ten minutes, the extremes being 0.305 and 0.706 kilogram calories. Heat loss by evaporation is not changed much by a cool dry or cool foggy atmosphere. It is increased by a hot (50 C) and dry (18 per cent) atmosphere and definitely decreased when the relative humidity of the hot (50 C) atmospheric air is increased (49 per cent). The mechanisms involved were studied.

Heat is lost from the respiratory tract by warming cool inspired air (convection, or  $h_c$ ). The mean value for  $h_c$  with the environment comfortable was  $0.122 \pm 0.004$  kilogram calories per square meter per ten minutes, the extremes being 0.088 and 0.180 kilogram calories. Heat loss by convection was not changed by changing the atmosphere to a cold dry or foggy one. When the temperature of the environment was raised to 50 C (relative humidity 18 or 49 per cent),

$h_c$  became a positive value, that is, heat was absorbed from the hot inspired air, thus tending to increase body temperature.

Heat is lost from the respiratory tract because of the excretion of carbon dioxide ( $h_{CO_2}$ ). Under comfortable atmospheric conditions, the mean rate of heat loss by the excretion of carbon dioxide was  $0.291 \pm 0.008$  kilogram calories per square meter per ten minutes, the extremes being 0.239 and 0.384 kilogram calories.

The value of  $h_{CO_2}$  is influenced only by the rate of excretion of carbon dioxide and therefore was influenced by the atmospheric temperature and relative humidity only so far as these factors influenced the rate of excretion of carbon dioxide.

The total heat loss from the respiratory tract ( $H$ ) is the sum of  $h_E + h_c + h_{CO_2}$ . From these components the mean rate of total heat loss from the respiratory tract was  $0.886 \pm 0.037$  kilogram calories per square meter per ten minutes, the extremes being 0.630 and 1.183 kilogram calories. The nature of the influence of  $H$  by the temperature and relative humidity is determined by the nature of the influence of these factors on the three components.

In the 27 normal young resting adults the total rate of heat production and, therefore, heat loss if the subject is in thermal equilibrium with his environment, was measured along with the heat loss from the respiratory tract. In a comfortable environment the mean rate of total body heat loss was  $8.08 \pm 0.19$  kilogram calories per square meter per ten minutes, the extreme being 6.62 and 10.77 kilogram calories. A hot dry or hot humid environment increased this value.

A single subject sitting in a comfortable environment and studied at frequent short intervals during seven hours of one day and at intervals of several days over a period of five and one-half months showed a remarkable constancy in the temperature and relative humidity of the expired air, rate of water and heat loss ( $H$ ,  $h_E$ ,  $h_c$  and  $h_{CO_2}$ ) from the respiratory tract, rate of total body heat loss and rate of irrigation of the respiratory tract with air. A heavy meal changed these values slightly. They were not significantly different during the hot summer or cool winter of subtropical New Orleans.

It is impossible to state definitely the nature of the expired air or water or heat loss from the respiratory tract without first defining at least the conditions of the air inspired, the type of respiration and the activity of the subject. These other factors influence the expired air considerably.

Mr. G. Morgani assisted in these studies.

# SOME OBSERVATIONS ON PRIMARY ATYPICAL PNEUMONIA

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Studies on primary atypical pneumonia, especially those of the past four years, have resulted in the awareness of a rather well defined clinical picture in this disease. Several authors, however, have presented series of cases differing considerably in their symptomatology. It is the purpose of this paper to describe a group of cases of the disease appearing during the first half of 1944 in Italy and to compare them with cases previously reported. A large number of the patients were evacuated from Anzio, and, in a sense, the outbreak may be regarded as localized. This series consists of 45 patients whose uniformity of symptoms is especially interesting as a form which the disease may take. Conditions governing the evacuation of casualties render it virtually impossible for one to reach any conclusions concerning epidemiology. It is my impression from conversation with patients that successive groups of persons in particular units were affected and that, at least under combat conditions involving exposure, chilling, fatigue and lowered resistance, the disease is apparently infectious, with a shorter incubation period than has been generally stated. This belief is strengthened by the reported higher incidence of the disease among station hospital personnel<sup>1</sup> as compared to that among other troops, the localized outbreaks in small units<sup>2</sup> and several small epidemics in hospitals<sup>3</sup>.

*Clinical Observations*—Almost invariably, the disease was well defined in onset. Only 5 patients admitted premonitory symptoms. Of these, 3 had "colds" and slight coughs of several days' duration. 1 complained of generalized aching and malaise for one day, and 1 stated he had been unwell for three to four weeks. However, in these patients as well as in the others, the onset of more severe disease was clearcut. This was marked by sudden chilly sensations and fever in

two thirds of the patients, accompanied by severe frontal headache. Not only was the last mentioned the most frequent early symptom, occurring in 78 per cent of the patients, but by its severity tended to draw attention away from symptoms referable to the chest, which early in the disease frequently showed no abnormalities on physical examination. Generalized muscular pains, most pronounced in the lower part of the back and the legs, were present at the outset in about half of the patients, a number of whom became aware of the pains a few hours prior to the chills and fever. An unusually high number (18, or 40 per cent) complained of pain in the chest at the onset. Unlike pains described in previous reports, which noted little pleural involvement,<sup>4</sup> in 13 of these patients the pain was unilateral and increased with inspiration. Only 5 described it simply as a soreness. Ten patients (22 per cent) mentioned coughing at the onset, at which time the cough was described as "slight" or "dry." Weakness, malaise, drowsiness, anorexia and nausea were present in variable degree in almost all the patients.

The course of the disease may be divided into two parts—an acute phase of five to seven days, until the temperature subsides, and a considerably longer recuperative phase lasting four to six weeks, during which the pulmonary tissue reverts to normal. During the first few days of the disease, there was little change in the picture. Repeated chilly sensations or chills, more frequently the former, continued irregularly for several days and invariably appeared, with fever, in those patients in whom they were not present at the onset. The temperature was of the irregularly elevated type, with wide daily variations at

1 Dingle, J. H., and others. Primary Atypical Pneumonia, Etiology Unknown, War Med 3 223 (March) 1943.

2 Idstrom, L. G., and Rosenberg, B. Bull U S Army M Dept, October 1944, no 81, p 88.

3 (a) Maxfield, J. R., Jr. Texas State J Med 35 340 (Sept) 1939. (b) Dingle, J. H., and Finland, M. New England J Med 227 378 (Sept 3) 1942. (c) Favour, C. B. New England J Med 230 537 (May 4) 1944.

4 (a) Campbell, T. A., Strong, P. S., Grier, G. S., III, and Lutz, R. J. Primary Atypical Pneumonia. Report of 200 Cases at Fort Eustis, Virginia, J A M A 122 723 (July 10) 1943. (b) Duggan, L. B., and Powers, W. L. U S Nav M Bull 40 651 (July) 1942. (c) Young, H. E., Storey, M., and Redmond, A. J. Am J M Sc 206 756 (Dec) 1943. (d) Primary Atypical Pneumonia, Etiology Unknown, War Med 2 330 (March) 1942. (e) Whiteley, J. H., Bernstein, A., and Goldman, M. J. Mil Surgeon 91 499 (Nov) 1942. (f) Kneeland, Y., Jr., and Smetana, H. F. Bull Johns Hopkins Hosp 67 229 (Oct) 1940. (g) Green, D. M., and Eldridge, F. G. Mil Surgeon 91 503 (Nov) 1942.

times. As a rule, the higher temperature continued for five to seven days and then fell by lysis over a three day period. Chart 1 indicates the frequency distribution of the duration of fever. Coughing was prominent and occasionally distressing in the first days of the disease. In addition to the 10 patients who complained of cough at the onset, 11 (24 per cent) began to cough on the second day, 7 on the third day and a few still later. As a rule, the cough was not severe and was either dry or productive of a small quantity of mucoid sputum at first, either subsiding or becoming more productive at about the time the temperature fell to normal. Seven patients (16 per cent) brought up a slightly blood-streaked sputum, in no case was the hemoptysis severe.

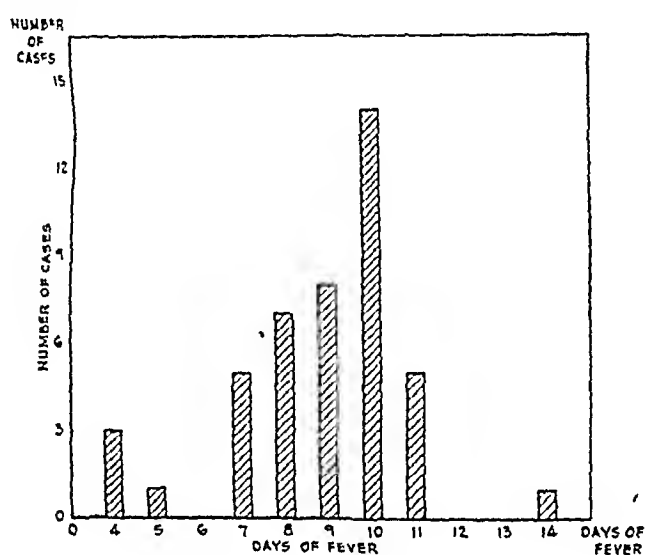


Chart 1—Duration of fever

The headache, after its initial severity, was variable both in intensity and in duration, lasting one to four days. The aggravation of headache by coughing suggested a relation to increased pressure of the cerebrospinal fluid in accordance with the observations of Dingle and his associates,<sup>1</sup> who relieved the headache in 7 patients by lumbar puncture. Similarly, the pain on breathing deeply tended to be transient, subsiding shortly. Other common systemic symptoms which occurred during the acute phase of the disease and paralleled its severity were weakness with lassitude in 17 patients (38 per cent) and anorexia (20 per cent). Seven patients vomited, 2 had seemingly spontaneous epistaxis.

Physical signs were neither prominent nor of specific diagnostic value. At the onset, patients were drowsy, with warm, flushed skin, either dry or covered by profuse perspiration. Cyanosis was uncommon, was rarely discernible and was evident in only 1 patient, who might have had an associated bacterial pneumonia. Respiration was often difficult and shallow, owing to pleural in-

volvement, but there was neither tachypnea, as seen in bacterial pneumonia, nor true dyspnea. The slightly increased respiratory rate gradually decreased as the acute picture subsided. A relative bradycardia was a constant feature during the acute phase, but as the temperature fell the cardiac rate rose in about half the patients. Similar observations were recorded by Green and Eldridge<sup>4c</sup> and Young, Storey and Redmond.<sup>4e</sup> The cause of this phenomenon is not known but may be related to the absorption of pathologic products from the tissues of the lung. Somewhat bleary, injected conjunctivas were seen fairly frequently, and 10 patients had injected pharynges, though only 4 complained of a sore throat. Lymphadenopathy was not a feature of the disease, a palpable spleen was twice encountered. Loss of weight was common and was prominent in 5 cases. Moreover, another aspect of recovery was evident in the patients' difficulty in regaining lost weight even after the appetite had returned and caloric intake was increased.

The paucity of signs referable to the chest, as observed by others,<sup>5</sup> has been—in contrast to the pronounced roentgenographic changes—one of the most remarkable features of the disease. The explanation probably lies in the fact that the pathologic process is primarily interstitial rather than within the air passages or alveoli<sup>6</sup>; this fact may likewise account for the absence of cyanosis. Physical examination of the chest revealed nothing abnormal almost throughout the entire course in 18, or 40 per cent, of the patients. Even when present, the signs were slow to appear, rarely being perceptible until the third day. At this time, some fine moist subcrepitant rales were discerned, best heard toward the end of inspiration, a smaller number of patients had simply diminished or roughened breath sounds. The presence of an impaired percussion note in a few was, as a rule, associated with larger and denser lesions, as seen roentgenographically. After seven to ten days from the onset the rales became coarser, moister and noisier, and rhonchi were heard. Some wheezing, which also appeared at this stage, persisted for several weeks. Evidence of frank consolidation was uncommon.

5 (a) Longcope, W. T. *Practitioner* **148** 1 (Jan) 1942. (b) Rhoads, P. S. *Radiology* **40** 327 (April) 1943. (c) Thompson, J. L., Jr. *M. Ann. District of Columbia* **12** 171 (May) 1943. (d) Correll, H. L., and Cowan, I. I. *U. S. Nav. M. Bull.* **41** 900 (July) 1943. (e) Lusk, F. B., and Lewis, E. K. *Dis. of Chest* **10** 19 (Jan) 1944. (f) Footnote <sup>4d</sup> Duggan and Powers<sup>4b</sup> Dingle and Finland<sup>3b</sup> Green and Eldridge<sup>4c</sup> Idstrom and Rosenberg<sup>2</sup>

6 Golden, A. *Bull. U. S. Army M. Dept.*, October 1944, no. 81, p. 64.

*Laboratory Observations*—From those laboratory procedures routinely performed, little of diagnostic value was found. The red blood cell count ranged between 4,000,000 and 5,000,000 per cubic millimeter, as did that of other patients. The white blood cell count during the acute phase of the disease was well scattered throughout the normal range of 5,000 to 9,000 per cubic millimeter. During the course of the disease, there was a perceptible increase in the white blood cell count, which on examination was seen to be due largely to an increase in lymphocytes between the fourth and sixth week (chart 2). The erythrocyte sedimentation rate appeared to be a reliable index of disease activity, its slow decrease correlating well with the gradual disappearance of roentgenologic evidence of disease. Though there

is the characteristic roentgenogram. The finding by Dingle and his associates<sup>1</sup> of 34 cases of "bronchitis resembling atypical pneumonia" (clinically) without roentgenographic changes does not detract from the value of the roentgenogram. The disease may occur in such forms that the roentgenogram is virtually the only evidence of its presence.<sup>7</sup> Fredd<sup>7a</sup> found its incidence to be 0.27 per cent of 23,465 roentgenograms of the chest taken of clinically well people. During the period my patients were studied, 2 of the hospital personnel examined roentgenographically for persistent cough of some weeks' duration were found to have patches of primary atypical pneumonia. In neither patient were other symptoms present. I have since seen an occasional patient whose only symptom was fever

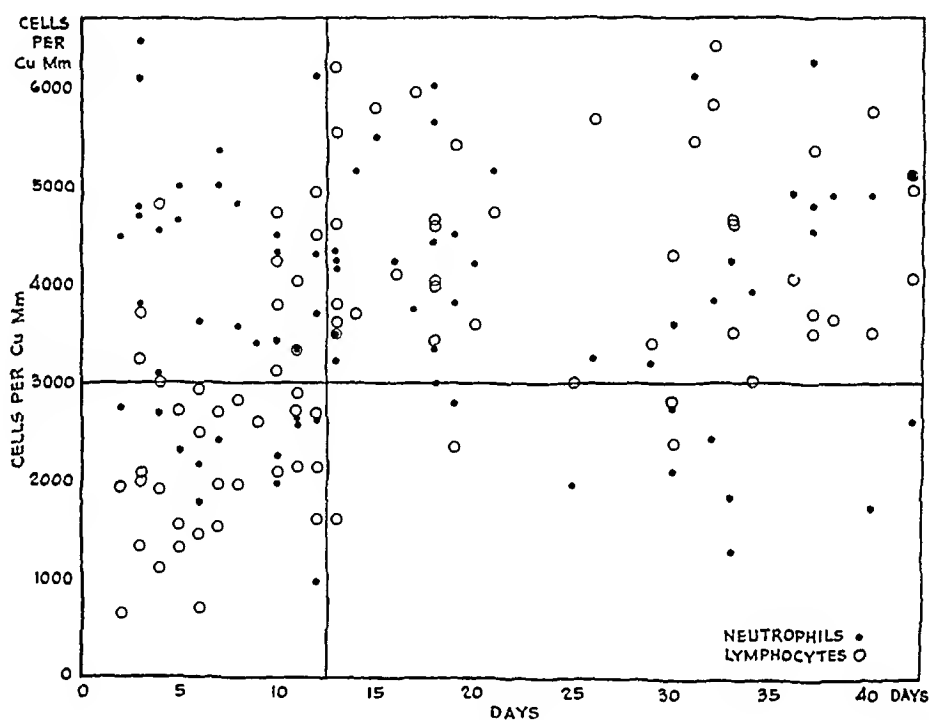


Chart 2—Rise in number of lymphocytes in course of primary atypical pneumonia

is considerable over-all variation in the results obtained (chart 3) for any 1 patient, the relative sedimentation rate from time to time is a valuable indication of recovery, second only to the roentgenogram itself.

Except for a variable degree of albuminuria in 11 patients and the presence of an occasional granular cast in the urine of 3 patients early in the disease, examination of the urine showed nothing abnormal.

Several attempts to demonstrate the presence of cold agglutinins were unsuccessful.

*Roentgenographic Observations*—In the lack of pathognomonic symptoms and with the dearth of physical signs in the chest, the roentgenogram assumes great importance in diagnosis. In fact, the principal criterion, almost the sine qua non,

Roentgenologic evidence of disease as a rule did not appear until two or three days after the onset. There was first an increase in bronchial markings, more pronounced at the hilar areas, followed shortly by irregular patches of increased density farther peripherally. The bronchial markings were also the last evidences of the disease to disappear. These areas of increased density varied from a soft mottling which in the upper lobes resembled early pulmonary tuberculosis to a denser, hazy opacity or glazed appearance seen in pulmonary congestion and which has also been said to be due to inflammatory pleural changes.<sup>4d</sup> The density was not

7 (a) Fredd, H. New York State J. Med. 41: 34 (Jan. 1) 1941. (b) Lusk and Lewis.<sup>5e</sup> Idstrom and Rosenberg.<sup>2</sup>

as pronounced as that seen in lobar pneumonia, again in consequence of the fact that the pathologic process is interstitial and does not produce a filling of the alveoli with dense cellular material. Resolution, in contrast to that of bacterial pneumonia, is prolonged, and increased bronchial markings and some parenchymal mottling may remain long after the patient is clinically well.

In over two thirds of the patients, only one patch of pneumonia could be detected on roentgenographic examination. Nine patients had two distinct areas of density and 1 patient three. Multiple areas were seen in 2 patients. The distribution of the lesions was similar to that described in previous reports,<sup>8</sup> with the lower lobes predominantly involved, as follows: right upper pulmonary field eleven times, left upper field six times, right middle and lower fields

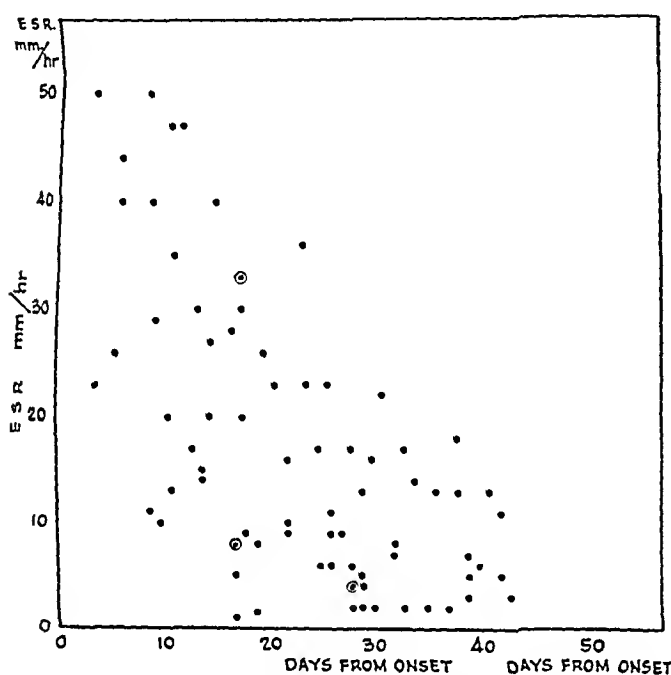


Chart 3—Fall in erythrocyte sedimentation rate during course of primary atypical pneumonia

seventeen times and left lower field twenty-one times. Where pulmonary tissue close to the interlobar pleura was involved, that pleura remained thickened, as mentioned by Bahlke,<sup>9</sup> this thickening was observed in 8 patients. It was my impression that when the upper pulmonary fields were involved the patients appeared to be more ill.

**Etiology**—No specific organisms could be isolated from those patients on whom bacteriologic studies were attempted. Viral causation was suggested by the absence of leukocytic response to the infection and by the failure of sulfonamide

therapy. Recent reports have strengthened the case for a theory of viral causation. Viruses have been isolated from normal mouse lungs which required only serial passage through other mouse lungs to become pathogenic.<sup>10</sup> This result suggests the possibility of a human reservoir of the virus among healthy persons. Serums of some patients in New York city gave positive neutralization reactions against psittacosis virus.<sup>11</sup> Not only have viruses been isolated from some patients,<sup>12</sup> but the Commission on Acute Respiratory Diseases<sup>13</sup> has been able to transmit the disease from throat washings and sputum of patients to volunteers. Since both untreated and filtered material were equally successful, a filtrable agent would appear to be responsible.

**Differential Diagnosis**—The lack of pathognomonic history or signs makes differential diagnosis difficult, especially in the early stages of the illness. The only diagnostic laboratory observation, the demonstration of an increased titer of cold agglutinins in the serum, is of limited value. They are frequently absent, as in my patients, and even when they occur their presence cannot be detected until after the acute phase of the disease has passed. These difficulties further emphasize the importance of the roentgenogram of the chest in establishing the nature of the illness. The disease closely resembles influenza in its onset and early course, in the presence of cough and signs referable to the chest, acute bronchitis is suggested. It is in several respects distinctly unlike influenzal pneumonia as seen during the last war,<sup>14</sup> the latter having been clinically more severe, often with a characteristic cyanosis, an elevated white blood cell count associated with secondary bacterial infection and a high mortality.

The severe frontal headache, chills and fever, generalized aching and unelevated white blood cell count frequently make it necessary, during the warmer months in Italy, to rule out malaria and sandfly fever.

10 Horsfall, F. L., Jr., and Hahn, R. G. *J. Exper. Med.* **71**: 391 (March) 1940.

11 Smadel, J. E. *J. Clin. Investigation* **22**: 57, 1943.

12 (a) Reimann, H. A. *Acute Infection of Respiratory Tract with Atypical Pneumonia. Disease Entity Probably Caused by Filtrable Virus*, *J. A. M. A.* **111**: 2377 (Dec 24) 1938. (b) Stickney, J. M., and Heilman, F. R. *Proc. Staff Meet., Mayo Clin.* **17**: 369 (June 17) 1942. (c) Beck, M. D., and Eaton, M. D. *J. Infect. Dis.* **71**: 97 (Sept) 1942.

13 *Transmission of Primary Atypical Pneumonia to Human Volunteers*. Commission on Acute Respiratory Diseases, *J. A. M. A.* **127**: 146 (Jan 20) 1945.

14 Reimann, H. A. *Bull. New York Acad. Med.* **19**: 177 (March) 1943.

8 Duggan and Powers,<sup>4b</sup> Whiteley, Bernstein and Goldman,<sup>4c</sup> Green and Eldridge,<sup>4g</sup> Dingle and others,<sup>1</sup> Young, Storey and Redmond.<sup>1c</sup>

9 Bahlke, A. M. *New York State J. Med.* **43**: 315 (Feb 15) 1943.

Most important from the viewpoint of therapy is the differentiation from pneumococcic and other bacterial pneumonias. Lobar pneumonia can usually be recognized as such in its sudden onset and marked pulmonary symptoms and signs, certain bronchopneumonias, especially those with a rapid infiltrative spread from the upper respiratory passages, are much more difficult to differentiate. In primary atypical pneumonia, the mode of onset, repeated chilly sensations, dry cough and frequent pain in the chest in the absence of distinct physical signs, combined with a normal white blood cell count, are characteristic. The roentgenogram is most important but may not show changes early in the course of the disease.<sup>15</sup> When doubt exists as to the nature of the pneumonia, the patient should be given the benefit of it in the form of a chemotherapeutic test. Though prevailing opinion considers the sulfonamide compounds of no value, there are some<sup>5c</sup> who urge their use to forestall secondary bacterial invasion. In any event, there is in the disease itself no contraindication to chemotherapy. If no response is obtained after two to three days of full doses and of adequate blood levels of the drug, it may be discontinued.

**Therapy**—I have not been aware of any therapy which considerably influences the course of the disease. Sulfonamide compounds have repeatedly been without effect. More recently, penicillin proved to be equally ineffectual. Plasma and whole blood were given to some of the more seriously ill patients, without noticeable improvement. Symptomatic treatment during the acute phase consisted of rest, high fluid intake (parenterally when necessary), alcohol sponges, codeine and acetylsalicylic acid for head and body aching and expectorants. When pleural pain was severe, procaine hydrochloride was injected locally at the proper level. Inhalation of oxygen was used in but a few cases for difficulty in breathing. During the slow convalescence, supportive therapy in the form of a high caloric diet supplemented by multivitamin capsules was given. Activity was increased gradually without necessarily waiting for complete roentgenologic resolution.<sup>16</sup> After being

allowed to be out of bed for some days, patients were permitted to go to mess and then to morning exercises for several days prior to discharge. I was not in a position to use roentgen ray therapy as recommended by Oppenheimer<sup>17</sup> and Hufford and Applebaum.<sup>18</sup> Readiness for discharge was based on the roentgenogram of the chest, the erythrocyte sedimentation rate and the general appearance, particularly as reflected in the gain in weight, of the patient. Hospitalization was usually of four to seven weeks' duration.

**Complications**—There were no fatalities in my series. Complications were uncommon. Eight patients were left with a thickened interlobar pleura and 1 with diaphragmatic pleural adhesions. One patient had a moderately severe earache without apparent cause, which subsided spontaneously. Two patients had herpes labialis, 2 had associated malaria. I did not encounter any thrombophlebitis or chronic productive cough.

#### REVIEW OF THE LITERATURE

A review of a number of reports on primary atypical pneumonia reveals, as indicated by Reimann, Havens and Price,<sup>19</sup> that the disease—it is one to regard all descriptions as a single disease entity—occurs in two principal forms: (1) a sporadic, more severe illness encountered mostly in civilian practice<sup>20</sup> and (2) an epidemic, milder form encountered in institutional life in schools, army camps and hospitals usually observed, therefore, among younger persons. This form is described by most authors.<sup>21</sup> It would seem that younger persons are better able to combat the disease and to avoid long sieges of illness and complications. Even in this young age group, the slowest recoveries were seen in a few of the older patients. The cases were of the milder type of the disease, and, though they resembled other series from army sources, they differed in a few respects.

17 Oppenheimer, A. *Am J Roentgenol* **49** 635 (May) 1943.

18 Hufford, C. E., and Applebaum, A. A. *Radiology* **40** 351 (April) 1943.

19 Reimann, H. A., Havens, W. P., and Price, A. H. Etiology of Atypical ("Virus") Pneumonias, with Brief Resume of Recent Discoveries, *Arch Int Med* **70** 513 (Oct) 1942.

20 Reimann.<sup>12</sup> Kneeland and Smetana.<sup>4f</sup> Longcope.<sup>3a</sup>

21 (a) Goodrich, B. E., and Bradford, H. A. *Am J M Sc* **204** 163 (Aug) 1942. (b) Haight, W. H., and Trolinger, J. H. *U S Nav M Bull* **41** 988 (July) 1943. (c) Smiley and others.<sup>15</sup> Maxwell.<sup>3a</sup> Duggan and Powers.<sup>4b</sup> Dingle and Finland.<sup>5b</sup> Whiteley, Bernstein and Goldman.<sup>4e</sup> Green and Eldridge.<sup>4g</sup> Dingle and others.<sup>1</sup> Correll and Cowan.<sup>5d</sup> Young, Storey and Redmond.<sup>4c</sup> van Ravenswaay and others.<sup>16b</sup>

15 (a) Smiley, D. F., Showacre, E. C., Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis. New Disease Entity, *J A M A* **112** 1901 (May 13) 1939. (b) McCarthy, P. V. *Radiology* **40** 344 (April) 1943. Thompson.<sup>5c</sup>

16 (a) Drew, W. R. M., Samuel, E., and Ball, M. *Lancet* **1** 761 (June 19) 1943. (b) van Ravenswaay, A. C., and others. Clinical Aspects of Primary Atypical Pneumonia. Study Based on 1,862 Cases Seen at Station Hospital, Jefferson Barracks, Missouri, from June 1, 1942 to Aug 10, 1943, *J A M A* **124** 1 (Jan 1) 1944.

It is probable that many cases diagnosed as influenza during World War I were actually cases of atypical pneumonia. At Fort Sam Houston, for example, one fourth of 1,000 patients with "uncomplicated influenza" had persistent basal rales, and roentgenographic examination revealed local areas of increased density in almost all this group.<sup>22</sup> Bowen,<sup>23</sup> in 1935, described the characteristic roentgenographic picture in what appears to have been a mild form of the illness, and the following year Allen,<sup>24</sup> again from Fort Sam Houston, reported 68 cases of "acute pneumonitis" with similar roentgenographic features. Clinically, the cases were characterized by a "benign course, few physical signs, and roentgenologic evidence of localized inflammatory process in the lung."

Primary atypical pneumonia, as described by the Commission on Pneumonia for the Surgeon General,<sup>4d</sup> bears many similarities to the illness in my patients as well as some points of difference. The described chilly sensations, dry cough later becoming productive, relative bradycardia, normal or slightly increased respiratory rate, involvement of the lower lobes with a few physical signs relative to the roentgenographic signs, normal white blood cell count, duration of fever and prolonged convalescence disproportionate to the apparent severity of the disease were all evident in this series. However, the gradual onset with only mild headache and absence of pleuritic pain differ from the symptoms of my patients. The cases of Moore, Tannenbaum and Smaha<sup>25</sup> were similar to some of mine in which the patients were less seriously ill, having febrile periods of two to five days with complete resolution in three or four weeks. In the 80 cases reported by Green and Eldridge,<sup>4e</sup> as in my own, the patients exhibited intense frontal headache, cough, pain in the chest and meager signs referable to the chest, one third of the patients had a mild tachycardia during convalescence. Though pain in the chest was present in 35 per cent of their patients, pleuritic pain was described as rare. Another series of cases of military origin, that of Whiteley, Bernstein and Goldman<sup>4e</sup> resembled mine in the lack of definite physical signs, the production of blood-flecked

sputum and fever of seven to ten days' duration. In these too, unlike others, pleuritic pain was rare, a less common feature here reported was a definite leukopenia in all but 1 case.

Duggan and Powers,<sup>4b</sup> from their experience with naval personnel, described an illness resembling that which I observed in its griplike onset, minimal physical signs with coarse rales after defervescence, relative bradycardia, roentgenographic changes, normal blood count and absence of complications. Their patients were apparently less severely ill than mine, requiring less hospitalization. No pleuritic pain or hemoptysis was encountered, and in three fourths of the patients, the chest was normal on physical examination. Coriell and Cowan,<sup>5d</sup> reporting 155 cases, described an abrupt onset with minimal physical signs in all patients and predominance of pathologic conditions in the lower lobes. Another report from naval sources by Haight and Trolengei<sup>21b</sup> described cases similar to mine.

In the study of Dingle and his associates<sup>1</sup> three fourths of the patients had a gradual onset of the illness and 35 per cent a preceding infection of the upper respiratory tract. Chilliness was experienced by 75 per cent, but only 13 per cent had shaking chills. Cough was present in all patients and blood-streaked sputum in 12 per cent. Pain in the chest was present in 44 per cent, in 18 per cent it was pleuritic in nature. Positive signs referable to the chest chiefly sticky, subcrepitant rales at the end of inspiration, were heard in less than half of the patients. The roentgenograms, similar to those of my patients, showed involvement of the lower lobe in 70 per cent. Stressed also was the lack of correlation between physical signs and extent of roentgenographic changes. The signs often appeared late, when the temperature had begun to subside. The white blood cell count remained normal as a rule. Duration of hospitalization averaged 31.7 days (compared with 36 days in my series). The only complication of any consequence was a chronic productive cough, suggestive of early bronchiectasis but not proved. Other complications reported from time to time, such as thrombophlebitis, pleural effusion and manifestations referable to the central nervous system, were not encountered. During the period of study, 34 cases of "bronchitis resembling atypical pneumonia," but lacking roentgenographic corroboration, were observed, these were considered to represent a mild form of the disease.

One of the most comprehensive reports is that of van Ravenswaay and others,<sup>16b</sup> based on 1,862 cases. In this group, the onset was sudden in one third and gradual in two thirds. Chilliness was experienced by 68 per cent but associated

<sup>22</sup> Hall, M. W. *Inflammatory Diseases of the Respiratory Tract*, in Ireland, M. W. *The Medical Department of the United States Army in the World War*, Washington, D. C., Government Printing Office, 1928, vol. 9, p. 152.

<sup>23</sup> Bowen, A. *Am J Roentgenol* **34** 168 (Aug) 1935.

<sup>24</sup> Allen, W. H. *Ann Int Med* **10** 441 (Oct) 1936.

<sup>25</sup> Moore, G. B., Jr., Tannenbaum, A. J., and Smaha, T. G. *Atypical Pneumonia in Army Camp*, *War Med* **2**:615 (July) 1942.

rigor by only 11 per cent. Pain in the chest was present in 70 per cent and seemed of pleural origin in 48 per cent. The value of the erythrocyte sedimentation rate as a means of evaluating the course of the disease was stressed—an observation with which I fully agree. A pertinent point concerning the length of hospitalization was made. Though complications occurred largely in those patients who were allowed to be ambulatory soon (four afebrile days), it was not necessary to wait until the roentgenogram showed complete clearing. Patients with two weeks of normal temperature and a low erythrocyte sedimentation rate could tolerate exercise without reactivation or impaired clearing of the roentgenographic picture.

An outbreak of 40 cases of the disease among hospital personnel described by Young, Storey and Redmond<sup>4c</sup> showed many features similar to the ones described here. Chilly sensations, persistent cough, headache and generalized aching were common. These authors stressed also the relative bradycardia with increase in the rate at lysis, an increase in respiratory rate only in extensive involvement, fever of five to eleven days, usual involvement of the lower lobes and a lack of complications. Another localized appearance of the disease, 40 cases representing 40 per cent of a company, was described by Idstrom and Rosenberg.<sup>2</sup> All cases appeared in ten days. As in this series, the picture included severe frontal headache, dry cough, seven to ten days of fever, few physical signs until the fifth or sixth day, a sputum negative for pathogenic organisms, absence of cold agglutinins and an elevated erythrocyte sedimentation rate whose fall correlated well with the clearance of the chest. Hospitalization lasted thirty to forty days, and there was no fatality.

The disease as described by Reimann,<sup>12a</sup> Kneeland and Smetana<sup>4f</sup> and Longcope<sup>5a</sup> appeared to be of the more severe variety with greater toxicity, longer duration, more complications and higher fatality. Longcope, in fact, divided his cases into three groups according to the severity of the disease, namely, mild, moderately severe and severe. The first group was the largest, included half his cases and most approximated the disease as seen in my patients. These severe forms of the disease occurred for the most part in sporadic cases among older persons in the civilian population.

#### CONCLUSIONS

Primary atypical pneumonia is an acute infectious, usually self-limited disease occurring in varying severity. In the milder form, there are two distinct phases of the disease, namely, a

short acute febrile period lasting seven to ten days and a prolonged interval of convalescence during which the pathologic process slowly recedes and the absorption of pathologic products coincides with an increase in heart rate and white blood cell count and a prolonged elevated erythrocyte sedimentation rate. Though the disease itself is old and has probably been identified in the preserved lungs of American Civil War soldiers, the growth of our understanding of the disease during the past five years stems historically from two facts.<sup>26</sup> The increased use of the roentgenogram has demonstrated a picture that is characteristic and differing in its development, course and resolution from that of bacterial pneumonia and, in some cases, has revealed the presence of the disease in the absence of other evidence. Also, the use of sulfonamide compounds has been followed by a condition leading to a better understanding of the disease. A larger number of patients with pneumonia were treated in the home, those patients who failed to respond to treatment were hospitalized. In short, relatively more patients with primary atypical pneumonia reached those institutions in which the disease could be best studied and segregated.<sup>14</sup> The high incidence of the disease in the services also added to the knowledge concerning it.

The nature of the pathologic process has, in several ways, made the disease difficult to diagnose. The lesions' being interstitial rather than exudative into the air spaces results in the absence of dyspnea, tachypnea and cyanosis and minimizes physical signs, thereby focusing attention away from the chest. Moreover, even though the clinician be well aware of the early symptoms and be prompted to order that a roentgenogram be made, he is apt to be misled by the delay in appearance of roentgenologic changes unless he repeats the study after several days. The tendency on viewing the first, normal roentgenogram is to regard the condition as an infection of the upper respiratory tract and to discharge the patient shortly after the fever has subsided, just when continued rest is of great importance in preventing the spread of the pneumonic process. A greater awareness of this condition is still necessary.

Proper treatment of the disease requires an understanding not only of the nature and high incidence of the illness but also of its pathology and of the lack of correlation between physical and roentgenologic signs and of the course of the disease process.

Lieutenant Colonel W. W. Bondurant Jr., Army of the United States, cooperated in this study.

# ACUTE PORPHYRIA

## CLINICAL AND PATHOLOGIC OBSERVATIONS

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With the increasing knowledge of the importance of porphyrin metabolism and with the increasing frequency with which porphyria has been reported, there has been widespread interest in this fundamental subject. There is lack of knowledge, however, of the biologic mechanisms involved as well as of the cause of the varied symptoms. In this connection I thought that the results of my observations, both clinical and pathologic, might be of interest.

The porphyrins are widely distributed in nature<sup>1</sup>. They form part of the complex molecule of hemoglobin, myoglobin and cytochrome. The porphyrins arise in the body during synthesis of hemoglobin rather than during its destruction, as had been previously assumed<sup>2</sup>. A number of excellent comprehensive reviews of the subject of porphyrins have appeared in the recent literature,<sup>3</sup> some of the reports being particularly pertinent to this paper.

Small amounts of porphyrin of the isomeric series I and II are excreted as coproporphyrin I and III in the urine of normal persons. While porphyrin I is not utilized and is excreted in the urine as coproporphyrin I, the porphyrin III which is not utilized, owing to its being synthesized in amounts greater than that required to enter into the formation of hemoglobin or owing to a possible toxic block,<sup>4</sup> is excreted as coproporphyrin III. In porphyria as well as in a great variety of other diseases, these pigments are excreted in amounts far above the normal range.

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1 Dobriner, K, and Rhoads, C. P. The Porphyrins in Health and Disease, *Physiol. Rev.* **20** 416-468 (July) 1940.

2 Nesbitt, S. Excretion of Coproporphyrin in Hepatic Disease, *Arch. Int. Med.* **71** 483-488 (April) 1943.

3 (a) Dobriner and Rhoads<sup>1</sup>. (b) Waldenstrom, J. Studien über Porphyrin, *Acta med. Scandinav.* 1937, supp. 82, pp. 1-254. (c) Watson, C. J. Porphyrins and Diseases of the Blood, in *Symposium on Blood*, Madison, Wis., University of Wisconsin Press, 1939, pp. 14-30. (d) Mason, V. R., Courville, C. B., and Ziskind, E. The Porphyrins in Human Disease, *Medicine* **12** 355-439 (Dec.) 1933.

4 Dobriner and Rhoads<sup>1</sup>. Watson<sup>3c</sup>. Nesbitt<sup>2</sup>.

The forms of porphyria have been classified into three broad groups: congenital, acute and chronic. While these represent a general classification, some striking variations in the symptoms may be observed, and occasionally the case may present features of more than one group. This variability was illustrated in the case to be described, which presented some of the clinical features found in congenital as well as in acute porphyria.

In congenital porphyria, the onset is usually early in life but may be delayed until the patient is 15 years of age. There is a familial tendency. Photosensitivity is prominent, and a chronic bullous or erythematous dermatitis with exacerbations in the spring and summer is present. The urine is burgundy red at times, with large amounts of coproporphyrin I or uroporphyrin I or III. At autopsy, very little may be observed except a pinkish discoloration of the teeth and bones.

In acute porphyria the attacks are frequently characterized by a sudden onset, with severe abdominal pain and obstipation. The symptoms<sup>3b</sup> may be classified into three types: (1) abdominal, (2) nervous and (3) mental. They may occur singly or may be combined. Frequently the acute attacks are ushered in with the menstrual period, or they may occur post partum. It has recently been pointed out<sup>5</sup> that acute porphyria is as much a familial disease as congenital porphyria, with the underlying mechanism an inborn error of pigment metabolism.

Hypertension and tachycardia are frequent. There is often a low grade fever, and leukocytosis may be present. Nervous symptoms, such as severe pains and weakness in the extremities, bulbar weakness and a symmetric paralysis of the lower motor neuron type with flaccidity and loss of reflexes, may develop<sup>6</sup>. A classic Landry

5 Nesbitt, S. Acute Porphyrin, *J. A. M. A.* **124** 286-294 (Jan. 29) 1944.

6 Hoagland, P. I. Acute Porphyrin. Report of Two Cases with Neurologic Manifestations, *Proc. Staff Meet., Mayo Clin.* **17** 273-281 (May 6) 1942.

type of paralysis has been described. With the development of neurologic manifestations, a mortality as high as 75 per cent may be expected. Remissions and improvement do occur, particularly with the abdominal type, in which recurrences are frequent. Occasionally various mental changes<sup>6</sup> are observed. The urine may be burgundy red, or it may be amber, but on exposure to sunlight it changes to the characteristic color. A simple test for porphyrins in the urine has been recently described by Watson and Schwartz.<sup>7</sup> The increased porphyrins in the blood may be detected by a number of methods. Coproporphyrin I and III have been observed in the feces.<sup>8</sup> The pathologic observations are meager, but the most extensive descriptions have been presented by Waldenstrom<sup>3b</sup> and Mason, Courville and Ziskind.<sup>3d</sup>

Acute porphyria has been further classified into acute toxic and acute ideopathic forms, however, these forms apparently present no fundamental clinical differences,<sup>3</sup> the differentiation being made on the history of an exciting etiologic agent. Chronic porphyria is not well characterized and possibly does not represent a distinct form but may constitute a mild form of either congenital or acute porphyria.

It was thought of interest to study the reaction of the capillaries, gastrointestinal motility, and blood chemistry and to attempt to correlate these factors with some of the protean symptoms of porphyria. Rusk and Howell<sup>8</sup> showed that in experimental animals injections of hematoporphyrin had a pronounced effect on the circulation, particularly the cutaneous circulation, with a gradual rise in blood pressure beyond the normal followed by a fall, vascular collapse and death. There was presented evidence that the hematoporphyrin combined slowly with a substance or substances in tissues and that this compound was formed in the dark as well as in the light. It was the action of light on this combination that gave rise to the injurious effects. The action of the porphyrins on the gastrointestinal tract has been variously ascribed by different authors to different mechanisms, that is, the disturbed function has been thought to be due to lesions of the sympathetic ganglions (Mason, Courville and Ziskind<sup>3d</sup>) or to a toxic effect on muscles which is not abolished by atropine (Dobriner and Rhodes<sup>1</sup>) or to the action on the autonomic nervous system.<sup>5</sup>

7 Watson, C J, and Schwartz, S. A Simple Test for Urinary Porphobilinogen, *Proc Soc Exper Biol & Med* **47** 393-394 (June) 1941.

8 Rusk, E N, and Howell, W H. Photodynamic Action of Hematoporphyrin, *Am J Physiol* **84** 363-377 (March) 1928.

## REPORT OF A CASE

The patient, a 20 year old woman, was referred to me by Dr M Waisman because of the sudden development of severe abdominal pains, nausea and persistent vomiting.

She gave a history of being entirely well until the age of 16, when, after the onset of menstruation, she noted the occurrence of a bullous eruption over the exposed portions of the body. The condition was worse in the spring and summer, when she blistered easily on exposure to the sun. The cutaneous condition was later diagnosed as epidermolysis bullosa.

In March 1940 she had her first attack of generalized abdominal pain and persistent vomiting. An exploratory operation was performed, and a normal appendix was removed. After the operation the complaints gradually subsided.

In October 1940 she had another attack of abdominal pain and persistent vomiting, and jaundice developed. This was associated with a mild psychotic episode. This acute phase persisted for a period of seven weeks, and the diagnosis of acute porphyria was established.<sup>9</sup> The urine was reddish brown and contained large amounts of coproporphyrin and uroporphyrin as the zinc metal complex. A decided increase of porphyrins was also demonstrated in the blood. The bilirubin of the blood increased to 19.8 mg, and the van den Bergh reaction was direct. The serum protein was 8 Gm per hundred cubic centimeters, and the albumin-globulin ratio was 1.1 to 1. Tests of sensitivity to light showed the patient to be sensitive to the far ultraviolet portion of the spectrum.

The urinary excretion of porphyrin varied considerably from time to time, and a urinary excretion of coproporphyrin up to 3 mg in twenty-four hours was reported<sup>10</sup> early in 1941.

When first seen, on May 29, 1941, in addition to having pains and vomiting of two days' duration, the patient felt cold in spite of the intense heat (the temperature ranging in the nineties), and she complained of severe pains in the knee joints. On physical examination the pulse rate was found to be 120, the temperature 99 F, and the blood pressure 130 systolic and 110 diastolic. The abdomen was soft, there was no rigidity or tenderness, and the peristaltic sounds were diminished. The remainder of the physical and neurologic examination showed nothing abnormal. As there is no specific treatment for acute porphyria besides general supportive measures, various attempts were made to control the course of the symptoms. The first day, the patient was given 10 cc of a 10 per cent solution of calcium gluconate by injection with no demonstrable effect, and morphine was given to control the pain.

The variations in blood pressure and pulse rate may be observed in figure 1. The next day, May 30, her condition remained unchanged. She was given 1 cc of a solution of ergotamine tartrate hypodermically, after which she felt warm and began to perspire, the abdominal pain persisted, however. The following day the vomiting diminished, otherwise the condition remained unchanged. She was then given atropine, 0.45 mg orally four times daily, with complete subsidence of the vomiting, however, the pains persisted. On

9 Nesbitt, S, and Watkins, C H. Acute Porphyria, *Am J M Sc* **203** 74-83 (Jan) 1942. Nesbitt, S. Personal communication to the author.

10 Cornbleet, T. Personal communication to the author.

June 1, trasentin (diphenylacetyl-diethylaminoethanol hydrochloride) tablets were substituted for the atropine. On the following day it was noted that the pains were worse and that the pulse rate and diastolic blood pressure were still elevated, with the pulse rate being 130 and the blood pressure 120 systolic and 96 diastolic. She was given 1 cc of a 1:2,000 solution of neostigmine bromide subcutaneously, and in one hour there was a definite diminution of the abdominal pains, which continued to subside. The next day, on examination, she showed a pronounced improvement, the pulse rate and blood pressure having dropped to normal. She complained of only an occasional pain. Another cubic centimeter of neostigmine solution (1:2,000) was administered, and the patient felt entirely well.

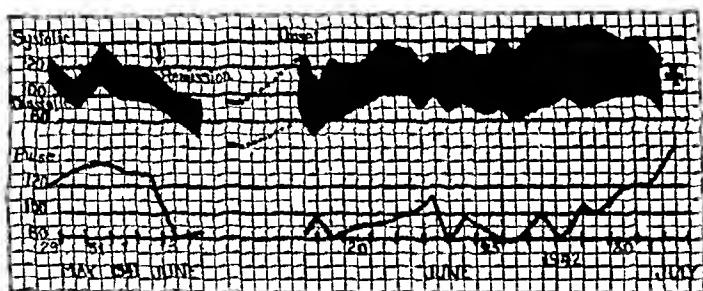


Fig 1—Daily record of the blood pressure and pulse rate

The significant laboratory observations were a pinkish color of the urine, which turned darker on standing, erythrocyte count, 4,200,000, hemoglobin content, 85 per cent, leukocytes, 5,500, neutrophils, 63 per cent, and lymphocytes, 36 per cent.

In the interval succeeding this attack, the patient was seen on two occasions. Except for her cutaneous lesions, she felt entirely well, and the examination showed nothing abnormal.

The observed acute attack was characterized by persistent vomiting, abdominal pain and diminished peristaltic sounds on auscultation. Further, there were present vasomotor phenomena, such as an increased blood pressure, particularly the diastolic, the sensation of severe cold in spite of the intense heat, lack of perspiration and articular pains. The question raised was whether the improvement which was observed after the injection of neostigmine bromide was a chance coincidence, for spontaneous remissions of the acute attacks do occur, or whether there was a definite causal relation, for the remissions do not occur as abruptly as did the one observed. In order to answer this question, it was decided to postpone reporting these observations until they could be confirmed either on other patients or on this patient during another attack. In addition, it was thought of interest to study reactions of the capillaries, gastrointestinal motility and blood chemistry and to attempt to correlate these with the symptoms. In another acute attack involving the same patient the following observations were made.

On June 17, 1942, the patient again had an acute attack similar to the one previously observed. The onset occurred with the menstrual period, as in the previous attack. The external temperature again was high, although she complained of being chilled. On physical examination the pulse rate was found to be 90 and the blood pressure 130 systolic and 90 diastolic. The skin was dry and the abdomen soft, and peristaltic sounds were absent. The patient was given 1 cc of a solution of neostigmine (1:2,000) hypodermically, after which she began to perspire, there was some

diminution of abdominal pain, and peristaltic sounds were heard over the abdomen. The articular pains were unaffected. On June 19 the condition was the same as that originally observed. She was given 1 cc of the neostigmine solution and 6 mg of mechoyl bromide, which produced severe vomiting, salivation, a feeling of heat replacing the feeling of cold, profuse perspiration and complete relief from the abdominal and the articular pains. There was a drop in blood pressure and an increase in pulse rate. After three hours the articular pains recurred.

On June 20 it was noted that after the injection the vomiting ceased, and it never recurred, considerable peristalsis was present over the abdomen. The patient was given 3 tablets of neostigmine bromide (15 mg each) daily and 1 cc of the solution by injection. The following day the abdominal pains recurred, with diminished peristalsis. After injection of 1 cc of neostigmine solution there was a diminution of pain and increased peristalsis.

For the next six days she continued to improve symptomatically. By June 28 the abdominal pains had subsided completely, and the patient felt well, however, the blood pressure was persistently elevated, being 148 systolic and 100 diastolic, and the pulse rate was rapid. There was an icteric tinge to the scleras. The next day she complained of some weakness in the arms and legs, and in the evening she spoke irrationally. The following day, June 30, a definite increase in muscular weakness was present. The weakness in the arms and legs was more pronounced in the proximal than in the distal segments. She could move only her toes, fingers and hands. Tendon reflexes and the Babinski sign were absent. Sensibility to pain was intact as well as the position sense in fingers and toes. She was given 1 cc of neostigmine solution and 1 mg of mechoyl, with a transient increase in muscular strength.

The patient became rapidly weaker, the pulse rate increased. Finally she showed difficulty in phonation, Cheyne-Stokes respiration developed, and she died on July 2, 1942.

**Laboratory Observations**—The observations are summarized in the table. In addition, the blood exhibited a red fluorescence indicative of the presence of porphyrin.<sup>11</sup> The value for serum protein was elevated, as was evidenced in a previous attack.<sup>11</sup>

The albumin-globulin ratio of 11 to 1 was also similar to that observed in a previous attack. After the

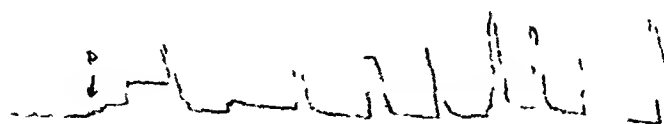


Fig 2—Kymographic record of gastric contractions. Record to the left shows gastric atony, after P (injection of 1 cc of 1:2,000 solution of neostigmine bromide) gastric contractions are seen. The white dots below represent time in minutes.

administration of mechoyl and neostigmine, the only significant change in the blood chemistry was an increase in the blood sugar.

An interesting observation was the reduction in the coagulation time (measured by Howell's method). Al-

11 Mason, H. L. Personal communication to the author.

though there was no evidence of thrombosis at autopsy, difficulty was experienced in inserting the needle into the peripheral veins while the patient was under observation

*Gastric Motor Activity*—At the onset of the last attack, before any medication was administered, a balloon was passed into the stomach in order that a recording of gastric contractions might be made. Varying reports of increased or diminished activity as observed fluoroscopically may be found in the literature.<sup>3</sup> The kymographic tracing may be observed in figure 2. During a sixty minute control period, the stomach remained dilated, and no gastric contractions were recorded. After the injection of 1 cc of neostigmine solution (1/2,000) in one and one-half minutes, gastric contractions were recorded, which increased in amplitude to reach a maximum. At first the waves were regular, and then they became irregular, although the height of the contractions remained the same.

*Observations on the Capillaries of the Skin*—The capillaries were observed through a capillary microscope. At the onset, in observations on the hand under low mag-

nification, the skin appeared pale, and the capillaries appeared either as faint violaceous loops or as dots. From one to three capillaries were visible per low power field. On the nail bed four capillaries were visible per low power field. They were short and extremely dilated and presented the picture of stasis. In only one of the four capillaries in a field was movement of blood seen. In some of the capillaries an aneurysmal dilatation was present. Within a short time after the injection of solution of neostigmine, very little change in the capillaries was seen. A number of hours later considerable capillary activity was observed, and again a few showed an aneurysmal dilatation. Although the capillaries were slightly increased in number, they were still much fewer than the number observed in the normal skin.

After the injection of both neostigmine and mechohyl solution, a pronounced increase in the number of capillaries was visible, the number increased to fifteen to twenty per low power field. They were of various shapes and showed considerable activity. On the nail bed many capillaries were seen, they were tortuous

Results of Determinations on the Blood

	Blood p <sub>H</sub>	Serum Protein (Refrac- tometer)	Serum Globulin	Serum Albumin	Dextrose	Calcium	Non protein Nitrogen	Coagulation Time (Howell's Method)	White Blood Cells	Red Blood Cells
June 18, 1942	7.43	9.49	3.60	4.00	89					
	7.42	8.96			89	8.69	28	40 sec		
After neostigmine	7.42	8.68			95			2 min	5,050	4,390,000
June 19, 1942	7.34	9.50			109			1 min 50 sec	4,000	4,220,000
After neostigmine and mechohyl	7.46	9.90			138			35 sec	6,500	4,600,000

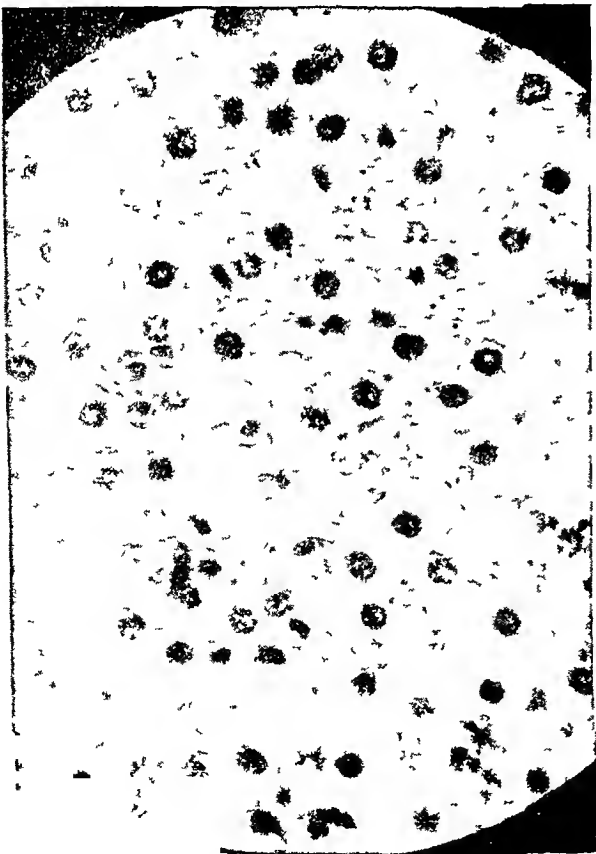


Fig 3—Photomicrograph of liver. Area of severe degenerative changes, sharply demarcated, is seen in the lower half of the field. (× 400)

and active. Even though they were dilated, red blood cells could be observed moving rapidly along.

*Autopsy Observations*—Gross observations revealed very little except a pinkish tinge of the tissues. The cartilage and the tissues of the breast were pink, and the bone presented reddish discolorations. The brain and spinal cord were reported by Dr Percival Bailey as being essentially normal. Microscopically, the liver showed diffuse degenerative changes, extreme granular cytoplasmic swelling and some vacuolation, with small localized areas of normal hepatic tissue. The hepatic cells in both the normal and the degenerated areas showed a yellowish pigment, with the amount of pigment being much less in the normal areas. The Kupffer cells were swollen and filled with a non-iron-containing pigment. Some of the hepatic changes may be observed in the photomicrograph (fig 3).

In the kidneys a number of the glomeruli showed a definite thickening of Bowman's capsule, otherwise, there were no significant changes.

Except for focal areas of bronchiolar pneumonia in the lungs, the other organs were normal.

COMMENT

The primary disturbance was a decided increase of the porphyrin in the blood. Coproporphyrin was excreted by the liver and kidneys, the liver being the more important organ of excretion.<sup>12</sup> Severe parenchymatous damage to

12 Nesbitt,<sup>2</sup> Nesbitt, S., and Snell, A. M. The Excretion of Coproporphyrin in Hepatic Disease. I

the liver was observed, with focal areas of relatively normal hepatic tissue remaining. With increasing parenchymatous hepatic damage, massive amounts of coproporphyrin were excreted in the urine by a mechanism similar to the excretion of bile pigments.<sup>12</sup>

The pressor episode, that is, the episode characterized by elevated blood pressure, sensation of cold and increased pulse rate, was probably a result of the extreme capillary spasm observed in the skin. Injury to the capillaries in the form of aneurysmal dilatations was observed. While no similar observations have been reported in the literature, Waldenstrom<sup>3b</sup> has reported changes in the arterioles in the form of subacute inflammatory changes, medial necrosis and sclerosis in several cases of porphyria. These aneurysms in the capillaries of the skin may be the result of the long-continued action of the porphyrins or the result of the interaction of sunlight on the tissues by a mechanism similar to that described by Rask and Howell.<sup>8</sup> The bullae arising in the skin as a result of exposure either to sunlight or to direct trauma may be related to the increased permeability of the capillaries, which in turn is the result of the injury to the capillary. Further studies are necessary to answer this question. The pains in the joints appear to have been due to capillary spasm with possible microscopic hemorrhages, for with release of the spasm immediate relief of the pain was observed.

At the same time that the capillary spasm was observed, a noticeable disturbance in gastric contractility was seen in the form of a prolonged period of atony, interrupted only by a brief rush of reverse peristalsis. In addition, there was an absence of peristaltic sounds over the abdomen. Immediately after the injection of neostigmine solution, the resumption of gastric contractions was recorded. The action on the capillaries was less noticeable. With the combined injection of mecholyl and neostigmine solutions, a pronounced reaction occurred, with definite capillary dilatations and gastric and intestinal contractions. Associated with these there was complete symptomatic relief of varying duration. As the reported action of neostigmine is to inhibit the destructive action of cholinesterase on acetylcholine and the action of acetylcholine (to which mecholyl is closely related) is manifested by parasympathetic stimulation and is necessary

for the transmission of nervous impulses,<sup>13</sup> the question arises as to the action and the site of action of the porphyrins as well as to their relation to the action of the drugs just mentioned.

While considerable research must be done to explain the action of the porphyrins on the nervous system, there is evidence to suggest several hypotheses. The porphyrin may produce a block in neuromuscular transmission and inhibit the action of acetylcholine at synapses, parasympathetic nerve endings and myoneural junctions and in the blood. In this connection, while the porphyrins circulate in the blood, the assumption of specificity and localization of action must be made. In support of this hypothesis may be cited by analogy the report of Kabat and Knapp,<sup>14</sup> who observed many examples of localization and specificity of the action of neostigmine in patients with poliomyelitis, although the drug is presumably distributed evenly throughout the body. Further support of the concept of a toxic block might be assumed in the results of recent observations in myasthenia gravis,<sup>15</sup> concerning which it is believed that the muscular weakness is due to some substance in the blood, possibly secreted by the thymus gland, which produces a block in neuromuscular transmission and inhibits the normal action of acetylcholine on voluntary muscle. The action of neostigmine in myasthenia gravis, according to this assumption, has been thought to produce some antagonistic effect on this inhibiting substance and to restore the normal release and rate of hydrolysis of acetylcholine. A possible action of the porphyrins may be to interfere with the control of the rate of hydrolysis of acetylcholine and with its relation to cholinesterase. Another possibility is that the porphyrins may interfere with the mechanism of synthesis and release of acetylcholine as postu-

13 Sollmann, T. A Manual of Pharmacology, ed 6, Philadelphia, W. B. Saunders Company, 1942. Lorente de N6, R. Liberation of Acetylcholine by the Superior Cervical Ganglion and the Nodosum Ganglion of the Vagus, *Am J Physiol* **121** 331-349 (Feb) 1938. Nachmansohn, D., and Meyerhof, B. Relation Between Electrical Changes During Nerve Activity and the Concentration of Choline Esterase, *J Neurophysiol* **4** 348-361 (July) 1941.

14 Kabat, H., and Knapp, M. D. The Use of Prostigmine in the Treatment of Poliomyelitis, *J A M A* **122**:989-995 (Aug 7) 1943.

15 Wilson, A., and Stoner, H. B. Myasthenia Gravis. A Consideration of Its Causation in a Study of Fourteen Cases, *Quart J Med* **13** 1-18 (Jan) 1944. Harvey, A. M., Lilienthal, J. L., Jr., and Talbot, S. A. Observations on the Nature of Myasthenia Gravis. The Effect of Thymectomy on Neuromuscular Transmission, *J Clin Investigation* **21** 579-588 (Sept) 1942.

Urinary and Fecal Excretion as Correlated with Parenchymatous Hepatic Damage, *Arch Int Med* **69** 573-581 (April) 1942, II Urinary and Fecal Excretion in Biliary Obstruction, *ibid* **69** 582-588 (April) 1942.

lated in recent reports<sup>16</sup> A third possibility is that the action of the porphyrins on the nervous system may be the result of a combination of these factors, that is, a possible interference with the mechanism of the formation and release of acetylcholine<sup>16</sup> and an interference with the control of the rate of the hydrolysis of acetylcholine and with its relation to cholinesterase<sup>13</sup> Variations must be assumed in the severity of action as well as in the site of action, whether the involvement be the peripheral or the central neurons, the preganglionic or the postganglionic nerves, the nerve synapses or the neuromuscular plates, for various reports have told of autonomic dysfunctions, of varying paralyses of upper and lower extremities with and without recovery, of successive episodes of transient paralysis, of ascending paralysis of the Landry type and of psychotic episodes In spite of the striking clinical alterations referable to the nervous system, repeated examinations at autopsy have failed to show any abnormal changes

My observations, both experimental and clinical, tend to emphasize the functional aspects of the nervous disorder and to suggest the hypothesis that the porphyrins may produce a block in neuromuscular transmission of varying degrees of severity, which may possibly interfere

16 Nachmansohn, D, and Machado, A L The Formation of Acetyl Choline A New Enzyme, "Choline Acetylase," *J Neurophysiol* 6 397-403 (Sept-Nov) 1943 Nachmansohn, D, Cox, R T, Coates, C W, and Machado, A L Action Potential and Enzyme Activity in the Electric Organ of *Electrophorus Electricus* II Phosphocreatine as Energy Source of the Action Potential, *ibid* 6 383-396 (Sept-Nov) 1943

with one or more of the phases of the action of acetylcholine on neurons, synapses, parasympathetic nerve endings and myoneural junctions and in the blood In addition, the action of the porphyrins on the blood vessels, organs and tissues of the body, as reported here and more extensively in the literature, must be considered

By way of criticism, it may be pointed out that the use of acetylcholine (or mecholyl) is dangerous and may be productive of more harm than benefit Greater experience in the use of neostigmine in the symptomatic treatment of this condition is necessary in order to evaluate its therapeutic efficiency

#### SUMMARY

An unusual case of acute porphyria was observed, and striking clinical and laboratory features as well as significant observations at autopsy were studied

Observations on the status of the capillaries of the skin during the acute attack were made, indicating extreme capillary spasm and evidence of injury to some of the capillaries in the form of aneurysmal dilatation In addition, definite alterations in gastric contractility were recorded

The action of injections of acetyl-beta-methylcholine chloride (mecholyl) and neostigmine bromide on the status of the capillaries of the skin, on gastric contractions and on altering the clinical picture was observed, as was the duration of the action

The use of neostigmine and mecholyl (particularly of the latter) in the symptomatic treatment of the acute phase of this disease may be dangerous and harmful

# RELATION OF NUTRITIONAL DEFICIENCY TO CARDIAC DYSFUNCTION

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That nutritional deficiency is associated with cardiac dysfunction has been recognized for almost sixty years. *Kakke*, which means "disease of the legs," was the subject of a paper by the Japanese author Takaki in 1886<sup>1</sup>. To others this disorder was known as beriberi. The Hollander Eijkman<sup>2</sup> and the Englishmen Fraser and Stanton<sup>3</sup> offered proof of the relation of beriberi to the consumption of a diet of polished rice. The elucidation of the cause of oriental beriberi is correlated with the development of knowledge concerning the vitamins.

## HISTORY AND CLINICAL DESCRIPTIONS OF BERIBERI

As is well known, beriberi was prevalent in the Philippines. Chamberlain<sup>4</sup> reported that among 5,000 Philippine Scouts there were always 100 to 600 incapacitated from beriberi. Their diet consisted essentially of 12 ounces (340 Gm) of beef, 8 ounces (230 Gm) of white flour, 8 ounces of potatoes or onions and 20 ounces (560 Gm) of polished rice. On changing the diet by substituting 16 ounces (450 Gm) of unpolished rice and 1 $\frac{3}{4}$  ounces (45 Gm) of beans for the 20 ounces of polished rice and by including 20 ounces of sweet potatoes, the number of cases of

the disease soon decreased to 50, then to 3, then to 2 and then to none.

Beriberi was also well known in the West Indies and in South America. In Newfoundland, where the cheapest food is white flour and where hunting and fishing in the winter are prohibited by the severity of the weather, the condition makes its appearance in the spring after a winter of a diet consisting mainly of white flour and tea. Not many cases have been described in the United States. In 1928, however, Scott and Herrmann<sup>5</sup> reported *maladie des jambes* in Louisiana. This was observed in the rice-producing parishes of that state among the rice-eating natives, who raised chickens, eggs and other foods but sold them, together with their unpolished rice, and bought with the funds so obtained polished rice. Their favorite and regular diet, *riz et sauce*, was composed of polished rice and bacon grease. These investigators also reported an outbreak of beriberi among the inmates of the Orleans Parish Prison, whose prison fare consisted of a stew of salt pork or beef and boiled hard cowpeas or beans or of carrots and soup and white bread, molasses and water. Milk or fresh vegetables or fruits were not served.

The outstanding symptoms in these persons were palpitation, dyspnea and edema, which led to a diagnosis of heart disease with congestive heart failure. In the rice belt the condition showed a predilection for men. When severe it ran a relatively short course, ending fatally within a few weeks. In the majority of cases the progress was slow. Just preceding or accompanying the appearance of edema of the lower extremities, palpitation developed. Dyspnea, at first barely noticeable, became extremely severe in time. Enlargement of the area of the heart, cardiac dilatation, valvular incompetence, a feeble, rapid soft and irregular pulse and often also an enlarged tender liver, accumulating edema, ascites, hydrothorax and hydropericardium ensued. These signs and symptoms

5 Scott, L. C., and Herrmann, G. R. Beriberi ("Maladie des Jambes") in Louisiana, J. A. M. A. 90, 2083 (June 30) 1928.

From the Department of Internal Medicine of the University of Utah.

Presented as guest speaker, at the Fifteenth Annual Postgraduate Symposium on Heart Disease, San Francisco, Oct. 27, 1944, under the auspices of the Heart Committee of the San Francisco Tuberculosis Association. The experimental studies on pigs described in this report were carried out with the aid of grants received chiefly from the Rockefeller Foundation, Parke, Davis & Company and the Upjohn Company.

1 Takaki, K. Results of the Preventive Measures taken Against the Occurrence of Kakke Among the Japanese Marine Prisoners, *Sei-i-Kwai M. J.* 41, 43, 1886, cited by Brandon, W. L. The Cause and Prevention of Beriberi, London, Rebman Co., 1907.

2 Eijkman, C. Polyneuritis and Beri-Beri, *Arch. f. Schiffs- u. Tropen-Hyg.* 15, 698, 1911.

3 Fraser, H., and Stanton, A. T. Studies from the Institute for Medical Research in the Federated Malay States, no. 10, 1909, no. 12, 1911, The Etiology of Beriberi, *Lancet* 1, 451, 1909, 2, 1755, 1910.

4 Chamberlain, W. P. Prevention of Beriberi Among Philippine Scouts by Means of Modification in Diet, *J. A. M. A.* 64, 1215 (April 10) 1915.

were accompanied with a feeling of weakness of the limbs and localized pains and tenderness in the muscles of the calf. Efforts to extend the foot against opposition were weak, and the strength of the grip of the hand was diminished. Sensory disturbances and diminution or absence of deep tendon reflexes completed the clinical picture. Frequently a history of nausea and vomiting was elicited, diarrhea occurred in a number of these persons, and in many pain on pressure in the epigastrium was noted. A presystolic gallop rhythm was observed occasionally. Electrocardiograms revealed small complexes, normal T waves in lead I or III, slight to moderate left ventricular preponderance and some slurring and slight aberrations in the ventricular complexes.

Keefer,<sup>6</sup> working in the Orient, described four varieties of beriberi—namely, (1) neuritic, (2) edematous, (3) cardiac and (4) mixed. A number of reports have appeared in past years describing cases of beriberi in various parts of the world. Among these should be mentioned those of Soma Weiss<sup>7</sup> and his associates in Boston. These workers described beriberi heart as occurring as often as once in every 160 admissions to the medical wards of the Boston City Hospital and as being more frequent than congenital heart disease and subacute bacterial endocarditis. Most of these patients were chronic alcoholic addicts. The cardiovascular disturbances were attributed to thiamine deficiency. They found that the circulatory failure in wet beriberi might involve either the right or the left side of the heart or both. Whereas Aalsmeer and Wenckebach described only "right-sided failure" Weiss also observed patients with orthopnea, cardiac asthma, pulmonary congestion and edema. Breathlessness, palpitation, tachycardia, gallop rhythm, murmurs and venous congestion were present. In severe involvement bounding pulsation of the arteries with pistol shot sounds developed.

Physiologic studies on patients with wet beriberi, particularly those with high venous pressures and edema, indicated that the arterioles were dilated, the utilization of oxygen in the venous blood was small and the velocity of blood flow was absolutely or relatively rapid. The vital capacity of the lungs was often severely reduced.

Dock<sup>8</sup> described 5 cases of congestive heart failure of obscure cause, in which there were re-

curring periods of dyspnea as well as embolic accidents involving the systemic and pulmonary circuits. In these cases pronounced cardiac hypertrophy and mural thrombi in the auricles and ventricles were found, but there was no evidence of endocarditis, myocarditis, coronary disease or arteriolar sclerosis. The diets of these persons had been poor. One of them recovered when fed a "high calory, high vitamin" diet but died in a later episode when he was given a "low salt, cardiac diet." A somewhat similar case was the subject of a clinical pathologic conference at Stanford University<sup>9</sup> and was discussed by Dr. Tinsley Harrison. In this case the heart failure was chronic, it was resistant to digitalis and, peculiarly in view of the alleged causation, also unresponsive to thiamine.

Aalsmeer and Wenckebach<sup>10</sup> ascribed the cardiac enlargement found in patients with wet beriberi to edema of the cardiac musculature. Newcomb,<sup>11</sup> on the other hand, could not demonstrate any increase in fluid and considered the cardiac enlargement to be true hypertrophy. Weiss stated that postmortem studies revealed a moderately or severely dilated heart without coronary or endocardial disease. In some cases of fatal circulatory collapse the cardiac dilatation was lacking. In certain instances myocardial hypertrophy was observed. Microscopically, interstitial edema, or collagen, and hydropic degeneration as reported by Wenckebach<sup>10</sup> was noted, but in other cases no microscopic changes were found. In 2 of Dock's cases<sup>8</sup> small patches of fibrous scarring of the left ventricle were described. In the case of Rytand and Cox,<sup>9</sup> there was no evidence of recent muscular injury, and most of the myocardium was free of scars. Here and there a small dense scar contained a group of lymphocytes.

#### CAUSE OF BERIBERI

That these cases represent the effects of nutritional deficiency is suggested by strong circumstantial evidence. The relation of dietary deficiency to beriberi has by no means been readily accepted, however. McCarrison,<sup>12</sup> for example, suggested that the disease may have a bacterial

9 Rytand, D., and Cox, A. J. Clinical Pathological Conference, Stanford M. Bull. **2** 86, 1944.

10 Aalsmeer, W. C., and Wenckebach, K. F. Herz und Kreislauf bei der Beriberi-Krankheit, Wien Arch. f. inn. Med. **16** 193, 1929.

11 Newcomb, C. Water Content of Heart Muscle in Beriberi Columbarum, Indian J. M. Research **17** 721, 1930.

12 McCarrison, R. Pathogenesis of Deficiency Disease, Indian J. M. Research **6** 275, 1919.

6 Keefer, C. S. The Beriberi Heart, Arch. Int. Med. **45** 1 (Jan) 1930.

7 Weiss, S. Occidental Beriberi with Cardiovascular Manifestations, J. A. M. A. **115** 832 (Sept 7) 1940.

8 Dock, W. Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, Tr. A. Am. Physicians **55** 61, 1940.

causation. In one review on the subject<sup>13</sup> as many as twenty-two different theories were advanced to account for it. In time the weight of evidence has come to favor those who hold to the nutritional causation. Even if one accepts this, however, it is necessary to demonstrate the exact nature of the deficiency. A diet composed chiefly of polished rice or the poor diet of the person with chronic alcoholism is lacking in many dietary essentials. Certainly the protein and the vitamin content of such diets are low. Many writers have attributed the edema to protein deficiency. With the recognition of vitamin B and later of a thermolabile fraction, vitamin B<sub>1</sub>, the manifestations of beriberi came to be attributed to lack of this dietary essential. As the multiplicity of the vitamins of the B complex has come to be recognized, it has become apparent that beriberi is a multiple nutritional deficiency. I have offered evidence that the nerve degeneration which may occur in this condition may not be due to lack of thiamine.<sup>14</sup> My remarks here will be confined, however, to the cardiac aspects of beriberi.

Weiss,<sup>7</sup> as well as a number of other writers, has described the rapid improvement occurring in cases of wet beriberi when thiamine is given to the patients. This, it is claimed, is much more dramatic than the changes which follow simple rest in bed or rest supplemented by treatment with digitalis and mercurial diuretics.

The etiologic role of thiamine in relation to the wet form of beriberi would be more convincing, however, if it were supported by experimental evidence. Experiments on human beings are naturally few. In those carried out by Williams and his co-workers<sup>15</sup> neither acute, severe deprivation nor moderate, prolonged deprivation of thiamine produced the classic syndrome of beriberi. Minor electrocardiographic changes were observed in a few of the subjects, low blood pressure and vasomotor instability were noted in all. Obviously the extent to which a deliberately produced deficiency can be carried in human

beings is limited. One limitation may be production of thiamine by bacteria growing in the intestines and absorption of the vitamin from the bowel, as the studies of Najjar and Holt<sup>16</sup> suggest.

#### EXPERIMENTAL THIAMINE DEFICIENCY IN ANIMALS

Current views as to the effects of thiamine deficiency in animals are based chiefly on studies in which animals were fed yeast which had been autoclaved or was otherwise treated with the object of destroying thiamine. Such experiments depended on the concept that vitamin B consists of only two parts, the thermolabile and the thermostable, and that by autoclaving the first of these is destroyed. When thiamine was discovered, it was assumed that it was the thermolabile B vitamin. It is now well known that the vitamin B complex consists of ten or more different factors. There is some evidence that in autoclaving yeast more than thiamine is destroyed.<sup>14</sup> It does not follow, therefore, that symptoms and signs developing in animals fed autoclaved yeast are necessarily due to lack of thiamine.

My own studies in thiamine deficiency were not attempted until most of the newer B complex vitamins were available in crystalline form and until I had shown that excellent growth and development take place in swine when they are given a basal diet consisting of casein, sugar, lard and minerals, supplemented with eight crystalline B vitamins and cod liver oil.<sup>17</sup> By failing to give one of the B vitamins or by giving only subminimal amounts, it has been possible to produce deficiency of thiamine or of riboflavin or nicotinic acid or pyridoxine or pantothenic acid. The effects of deficiencies of these vitamins in swine have been described in papers from this laboratory. It has been possible to demonstrate well defined cardiac changes in pigs given inadequate amounts of thiamine.<sup>18</sup>

The outstanding symptoms of acute thiamine deficiency in pigs have been failure of appetite,

13 Vaughan, V. C. Beriberi, in Vaughan, H. F., and Palmer, G. T. *Epidemiology and Public Health*, St. Louis, C. V. Mosby Company, 1922, vol. 2, p. 65.

14 Wintrobe, M. M., Follis, R. H., Jr., Humphreys, S., Stein, H. J., and Lauritsen, M. Absence of Nerve Degeneration in Chronic Thiamine Deficiency in Pigs, *J. Nutrition* **28** 283, 1944.

15 Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M. Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency and the Thiamine Requirement of Man. Further Observations, *Arch. Int. Med.* **69** 721 (May) 1942. Williams, R. D., Mason, H. L., Power, M. H., and Wilder, R. M. Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency in Man. Relation of Depletion of Thiamine to Development of Biochemical Defect and of Polyneuropathy, *ibid.* **71** 38 (Jan.) 1943.

16 Najjar, V. A., and Holt, L. E., Jr. Biosynthesis of Thiamine in Man and Its Implications in Human Nutrition, *J. A. M. A.* **123** 683 (Nov. 13) 1943.

17 Wintrobe, M. M., Miller, M. H., Follis, R. H., Jr., Stein, H. J., Mushatt, C., and Humphreys, S. Sensory Neuron Degeneration in Pigs, *J. Nutrition* **24** 345, 1942.

18 (a) Wintrobe, M. M., Stein, H. J., Miller, M. H., Follis, R. H., Jr., Najjar, V. A., and Humphreys, S. A Study of Thiamine Deficiency in Pigs, *Bull. Johns Hopkins Hosp.* **71** 141, 1942. (b) Follis, R. H., Jr., Miller, M. H., Wintrobe, M. M., and Stein, H. J. Development of Myocardial Necrosis and Absence of Nerve Degeneration in Thiamine Deficiency in Pigs, *Am. J. Path.* **19** 341, 1943. Wintrobe, M. M., Alcayaga, R., Humphreys, S., and Follis, R. H., Jr. Electrocardiographic Changes Associated with Thiamine Deficiency in Pigs, *Bull. Johns Hopkins Hosp.* **73** 169, 1943.

vomiting and sudden death. Poor growth was a less striking sign. A more or less chronic deficiency was produced in a number of animals by giving subminimal amounts. In such animals I observed weakness, shortness of breath and cyanosis. When in this state, the animals were reluctant to walk about, although obviously there was no paralysis. Examination of 1 such animal revealed the heart beat to be at a rate of 110 per minute, which is somewhat slow for a pig, but the sounds were of good quality, and no murmurs were heard. No rales were found in the lungs. This animal became cyanotic and staggered, fell, struggled stuporously to its feet, fell again on its side and lost consciousness. Just prior to death several convulsive movements were observed.

Another animal in a similar condition after a partial thiamine deficiency of two hundred and forty-six days' duration was reluctant to move about, and soon after he was exercised dyspnea became evident and audible. Some cyanosis was noted, and in time this became pronounced. It was especially noticeable in the ears, the snout and the lips. As time went on, it became more and more difficult for the animal to move about, and finally, after about forty-five minutes, it collapsed after a brief series of jerky movements in the hind quarters. When the animal recovered, it was exercised again. Exercise was followed again by collapse. Convulsive movements and finally death occurred one hour after exercise had been started. Cyanosis and dyspnea had become extreme by this time.

Animals fed inadequate amounts of thiamine have been studied carefully with the aid of electrocardiographic apparatus. Studies of the electrocardiogram of normal pigs show the heart rate to range between 130 and 150 beats per minute, although it may occasionally be as low as 100 and rarely as rapid as 160. The rhythm in my animals was sinuauricular with slight or moderate sinus arrhythmia. Normal electrocardiograms or a moderate tendency to left axis deviation was observed, and only once was a right axis deviation recorded. The PR interval ranged between six hundredths and twelve hundredths of a second. The P waves as measured in lead II were usually four hundredths to six hundredths of a second in duration and 1 to 2.2 mm in voltage. The duration of the QRS interval was four hundredths to six hundredths of a second, rarely eight hundredths. The T waves varied considerably. In general the T wave in lead I was more often inverted than upright, whereas in the other leads the T wave was usually upright.

In thiamine-deficient pigs two outstanding abnormalities were noted, namely, bradycardia and prolonged conduction time or even dropping of QRS complexes.

It has been claimed that bradycardia results from inanition rather than from the lack of thiamine specifically. We have compared the heart rates of thiamine-deficient pigs with those of animals deficient in other B vitamins. In such animals, the impairment of growth was in many instances much greater than in the thiamine-deficient pigs. We have also made observations on animals given diets that were normal but greatly restricted in amount. In these animals some slowing of the heart rate was observed, but, except in 1 animal subjected to severe dietary restriction, the bradycardia was never as pronounced as in a number of thiamine-deficient pigs.

It is noteworthy that bradycardia was not constant in the thiamine-deficient pigs. Tachycardia occurred when they became excited, after the injection of atropine and when acute cardiac failure developed in association with thiamine deficiency.

Prolongation of auricular-ventricular conduction time was observed in a number of animals. In some there was only first degree auricular-ventricular block, with PR intervals ranging from thirteen hundredths to twenty-eight hundredths of a second. In other animals the ventricular complex was dropped (second degree auricular-ventricular block). The combination of bradycardia and dropping of QRS complexes sometimes caused extreme prolongation of the PR interval, even to two and sixty-eight hundredths seconds. For this animal, nine days later the record suggested auricular fibrillation. This reverted to a normal rhythm without treatment.

Other abnormalities occurred less frequently. In several animals the P waves, especially the P wave in lead II, became abnormally high and broad and sometimes were notched. Occasionally slight widening of the QRS complex was observed, and in a few animals there was a definite shift of the axis to the left. In 1 such animal nodal premature beats were observed. The normal variations in T waves make it difficult to evaluate changes in T waves in thiamine-deficient pigs. The most constant abnormalities appeared to be inversion of the T wave in lead IV.

The observations of my colleagues and me have indicated that the electrocardiographic changes observed in the hearts of these animals were influenced by the degree of thiamine deficiency. With severe deficiency in 1 animal, for example, bradycardia developed as well as complete block.

with ectopic ventricular rhythm. Frequent ventricular extrasystoles arising from multiple foci appeared. These abnormalities disappeared after administration of thiamine.

The injection of atropine sulfate into thiamine-deficient animals caused an increase in heart rate and improvement in auricular-ventricular conduction with reappearance of regular QRS complexes.

Pathologic changes in pigs dying in a state of cardiac failure have been distinct. In some of the animals the hearts appeared to be larger than they should have been for the size of the animal. This enlargement seemed to be due both to dilatation and to hypertrophy. In a few a small amount of serous fluid was found in the pericardial cavity. In certain animals pulmonary edema and pleural and peritoneal effusions were found as well. Microscopic examination revealed foci of necrosis in the auricular and ventricular musculature as well as in the cardiac septums. The lesions consisted of focal or diffuse necrosis of myocardial fibers. Such areas were infiltrated by leukocytes.

In animals dying soon after deprivation of thiamine, lesions were found in the auricles and not in the ventricles. In animals dying after longer periods of deficiency, lesions were observed in the ventricles as well as in the auricles. In no instances were pathologic changes found in the ventricles when they were lacking in the auricles.

In 2 animals in which episodes of thiamine deficiency had been observed at intervals during the course of the experiments, stains for connective tissue revealed scars indicative of former necrosis of the myocardium. It is noteworthy, however, that such scars were not always found in pigs which had survived through previous episodes of severe deficiency. It seems, therefore, that, while scars marking the sites of previous myocardial necroses may be found in some animals, the lack of such scars does not necessarily indicate that thiamine deficiency has not been present.

It might be pointed out here that the vagus nerves in these thiamine-deficient animals were normal. At one time it was suggested that the cardiac manifestations of beriberi are due to degeneration of the vagus nerves.

#### COMMENT

These studies of thiamine deficiency in pigs show conclusively, I believe, that a lack of thiamine produces serious effects on the heart. It does not necessarily follow that the same effects are produced in human beings. There is much evidence that striking differences exist in regard

to vitamin requirements for different species and even in regard to the type of abnormality produced in different species of animals by a deficiency of the same vitamin.

The clinical observations in beriberi, however, would make it seem likely that much of what has been observed in thiamine-deficient pigs with reference to the heart is applicable to human beings. Certainly in fatal cases of cardiac failure in which thiamine deficiency is suspected, careful examination of the musculature of the heart, particularly of the auricles, should be made. It should be pointed out that it is to be expected that in some instances of beriberi no lesions will be found. Judging by what is known of the function of thiamine, it is to be expected that a metabolic disorder of the myocardium may occur and may lead to dysfunction and that death may ensue before recognizable lesions have developed.

The evidence at hand suggests that thiamine deficiency impairs the function of the heart by reducing the energy available from the normal processes of carbohydrate metabolism in which thiamine plays a role. Bradycardia is associated with the altered metabolic conditions of thiamine deficiency. Tachycardia is probably the expression of a decompensated heart and also, perhaps, the consequence of vasodilatation and reduced peripheral resistance. Finally serous effusions develop, and all the signs of cardiac failure appear. The evidence at hand also suggests that in thiamine deficiency vagal overaction is present.

The lesions we have found in thiamine-deficient pigs are unlike those that have been described as occurring in the beriberi heart. They suggest instead the types of cases which have been classified as isolated myocarditis, or Friedler's myocarditis. It is interesting to speculate whether in some instances these may have been examples of thiamine deficiency.

There is no agreement regarding the frequency with which heart failure due to thiamine deficiency may be encountered in the United States. Whereas Weiss observed many cases, others in Boston have recognized few. Besides the cases of acute failure, examples of chronic failure due to thiamine deficiency in which irreversible changes have occurred were reported from San Francisco. I have seen no convincing cases of the latter type and have recognized no more than 1 or 2 of the former. The recognition in human beings of cardiac failure resulting from thiamine deficiency would be greatly simplified if laboratory methods were available which could be relied on as indicative of such deficiency. Many workers, including me, have sought to attain this object, without the desired success. In my animals, thiamine excretion and thiamine

tolerance tests have been employed, the content of pyruvic acid in the blood has been measured, and pyruvic acid tolerance tests have been carried out<sup>18a</sup>. There are difficulties as yet, however, in the application of these procedures to the diagnosis of thiamine deficiency in human beings.

#### SUMMARY

A number of reports concerning the cardiovascular manifestations of beriberi were studied,

and the experimental evidence for the assumption that thiamine deficiency leads to impairment of cardiac function was assembled. In particular, recent studies of thiamine deficiency in pigs were considered. In these animals thiamine deficiency leads to profound changes in cardiac function and produces well defined anatomic lesions. Further investigation is required to demonstrate the role of thiamine in respect to the heart in human beings.

# EXTRAGENITAL CHORIONEPITHELIOMA IN THE MALE

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Of the malignant tumors occurring in the male, chorionepithelioma is considered to be rare. Some 200 cases have been recorded thus far in the entire literature. Its mode of origin is still uncertain, and many theories have been advanced to explain its presence in the male. These theories have recently been reviewed in a critical survey by Mathieu and Robertson<sup>1</sup>. Most authors accept the hypothesis advanced by Schlagenhauer,<sup>2</sup> that chorionepithelioma arises in a teratoma in which some structure having the morphologic value of an included ovum had differentiated into trophoblastic epithelium. Theoretically, teratomas may occur anywhere in the body, and they have been described in such areas as the mediastinum, the abdomen, the jaw and the sacrum. If chorionepitheliomas are to be considered as developing from teratomas, they need not always arise in the testes, although the tumors usually are found in these organs.

The existence in the male of chorionepithelioma primary in structures other than the testes has been doubted by such an authority as Prym.<sup>3</sup> However, at least 5 such instances of extragenital origin have been reported in the literature up to 1945.<sup>4</sup> Others have reported cases in which the

tumor was considered to be extragenital in origin but in which gross or microscopic examination of the testes was inadequate to exclude the possibility of a primary growth in these organs.<sup>5</sup> Only examination by means of serial section of the testes will eliminate the possibility that a primary growth in a testis was overlooked.

The following case is reported as further evidence of the existence of extragenital chorionepithelioma in the male.

E. C., a white man aged 30, was first admitted to Grace Hospital ward medical service on June 6, 1944. His chief complaints were pain in the left lumbar region of four months' duration and hemoptysis of two weeks' duration.

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From the Departments of Medicine and Pathology, Grace Hospital

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The patient had been in good health until one year prior to his admission, when he first noted slight swelling of the breasts lasting about one week and then subsiding spontaneously. Six months before his entry into the hospital, he experienced a dragging sensation in the left testis, at which time examination by his family physician disclosed a varicocele, for which a suspensory was prescribed. Persistent aching pain in the left lumbar region developed about four months before his admission to the hospital. Over this period there was a progressive loss of weight of 18 pounds (8.2 Kg). Two weeks prior to his entry a cough productive of blood-streaked sputum developed. At this time he also noted enlargement and tenderness of both breasts.

Physical examination revealed a pale, well developed, somewhat emaciated white man weighing 136 pounds (62.5 Kg). Both breasts were enlarged and tender, with prominent areolas and Montgomery follicles. No

increase in polymorphonuclear neutrophils. The reaction to the cephalin-cholesterol flocculation test was 2 plus. Wassermann and Kahn reactions of the blood were negative. Examination of the sputum revealed the presence of blood and a mixed flora of gram-positive and gram-negative cocci and bacilli, no tubercle bacilli were found. The reaction to the Friedman test of the blood and of the spinal fluid for presence of gonadotropic hormone was strongly positive.

Roentgenographic examination revealed the presence of several large rounded and well defined opaque masses in both pulmonary fields. Examination by intravenous pyelography demonstrated displacement of the left kidney laterally and forward by a large mass in the pre-aortic area. The series of gastrointestinal roentgenograms revealed displacement of the stomach downward, forward and laterally by a mass in the prevertebral area. The transverse colon and the splenic flexure were also displaced downward.

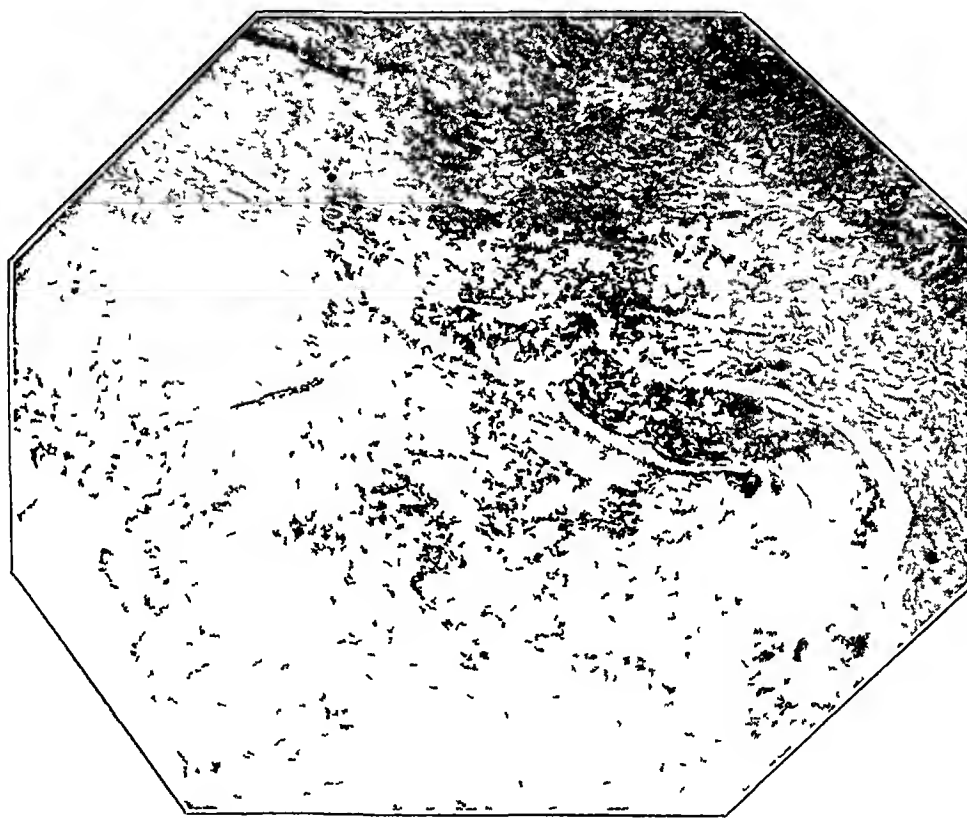


Fig 1—Chorionepithelioma, group of tumor cells in blood vessel of intestinal wall, ( $\times 35$ )

colostrum could be expressed. Several small nontender lymph nodes were present in both axillae. The blood pressure was 116 systolic and 60 diastolic. The abdomen was not distended, but definite tenderness was elicited in the left upper quadrant, where a large irregular firm mass was palpable. This mass extended to 3 fingerbreadths below the border of the ribs. It was immovable and seemed fixed to the posterior abdominal wall. No friction rub could be heard in this area. The liver and kidneys were not felt. Moderate tenderness was present in the left lumbar region. There was definite scoliosis of the vertebral column, with convexity directed toward the left. The right testis and epididymis were normal except for decreased sensitivity to pressure. The left testis was smaller and much softer than the right, but no nodules were palpated.

Urinalysis done at the time of the patient's admission to the hospital revealed a trace of albumin. The erythrocyte count was 4,390,000 per cubic millimeter and the leukocyte count 11,800 per cubic millimeter, with a slight

Because of the clinical and roentgenologic findings, a presumptive diagnosis of chorionepithelioma, probably primary in the left testis with metastases to the pre-aortic lymph nodes and lungs, was made. The left testis was removed through an inguinal incision. Serial sections of the testis were made in an effort to find the primary lesion. Gross examination revealed a very small hemorrhagic area, about 0.80 cm in diameter, in the lower pole of the testis. Sections through this area, however, showed no tumor growth, revealing merely fibrous tissue and a few pigment-containing cells. The cells lining the spermatic tubules were vacuolated. There was no evidence of spermatogenesis. In sections from different parts of the testis, clusters of polyhedral cells were found which were considered to be groups of interstitial cells. The sections were sent to Dr. Shields Warren, of Boston, who confirmed these observations and who wrote suggesting that they represented atrophy as a result of the output of female sex hormone. In view of the hormonal evidence and the distribution

of metastases, he concluded that the lesion was chorion-epithelioma, probably extragenital in origin but, however, developing from germinal epithelium originating in the urogenital ridge.

The patient was discharged to his home on July 7, 1944 and during the next five months was given intensive roentgen ray therapy in the department of radiology of Grace Hospital. Despite the fact that serial roentgenograms of the chest showed a definite decrease in the size of the pulmonary metastatic nodules and although the cough was less distressing, the patient became worse, requiring opiates for relief of the pain in the left lumbar region. Follow-up examinations in the tumor clinic during the course of the roentgen ray therapy revealed some decrease in the size of the mass in the left upper quadrant. Two weeks of occipital headaches accompanied with amblyopia culminated in an episode of sudden loss of consciousness. This was followed by complete amaurosis for a period of five

progressively weaker and died on the tenth day in the hospital.

Autopsy showed the following details.

**Gross Examination**—The body showed considerable emaciation. Both breasts were moderately enlarged. No fluid was found within the peritoneal cavity. The stomach and small bowel occupied their usual sites and on gross examination revealed no lesions. An irregular nodular mass, measuring 11 by 7 by 5 cm, was observed to lie anteromedial to the left kidney and below the left adrenal gland at the level of the second and third lumbar vertebrae. The mass was adherent to the periosteum of the vertebral bodies but did not involve the compact bone. It was distinctly separate from the kidney and adrenal gland and did not infiltrate these organs. Anteriorly it was covered with peritoneal reflections, and when these were divided the tumor mass could be dissected free and removed. On

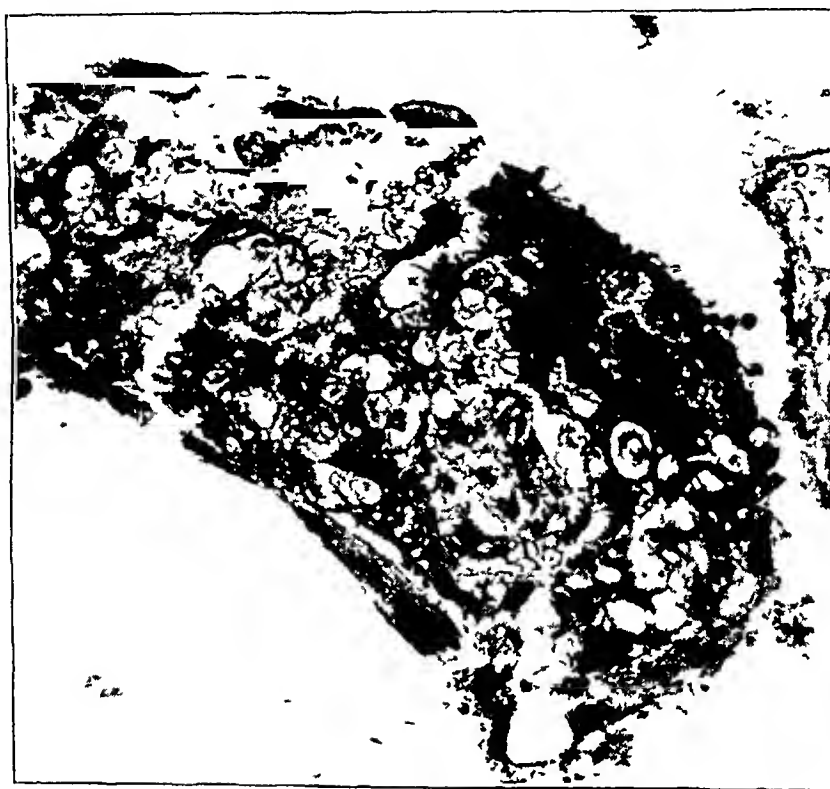


Fig 2—Same as figure 1 (high power,  $\times 325$ )

minutes and led to his readmission to the hospital on November 1, five months after his first admission.

His weight at that time was 114 pounds (52.5 Kg), a further loss of 22 pounds (10 Kg). Physical examination revealed a cachectic man, dyspneic and somewhat confused. The left pupil was larger than the right but reacted well to light. The fundi and visual fields were normal. Both breasts were enlarged, the right more than the left. The previously described mass in the left upper abdominal quadrant was unchanged. The left testis was absent. The right testis seemed smaller and softer than normal, but no nodules were felt. The erythrocyte count was 2,800,000 per cubic millimeter and the leukocyte count 9,500 per cubic millimeter, with 88 polymorphonuclear neutrophils. The reaction to the cephalin-cholesterol flocculation test was 1 plus. The result of the sulfobromophthalein sodium test for hepatic function was normal. Reaction to the Friedman test of the urine for gonadotropic hormone again was highly positive.

The patient complained of severe cough, dyspnea and lumbar pain and required heavy sedation. He became

cut section dense strands of pale red fibrous tissue surrounding small cystlike spaces and small areas of necrosis were seen to make up the entire structure.

The kidneys together weighed 295 Gm. When the capsule was stripped from the cortex of the right kidney, a few small dark lesions were seen which on section had the appearance of a metastatic tumor. The left kidney showed no tumor nodules. The renal vessels were free of tumor growth. On cross section, the adrenals showed no abnormalities. The prostate was not enlarged. The left testis was absent. The right testis was small, and on multiple cross section no nodules were encountered. There was no enlargement of the mesenteric, parailiac or inguinal nodes.

The large bowel contained much dark soft material, suggestive of old blood. An irregular dark polypoid mass, about 2 cm in diameter, was seen arising from the mucosa of the large bowel at the first part of the descending colon. There was no surrounding area of infiltration or necrosis.

The liver weighed 1,340 Gm. On cut section, no gross evidence of malignant infiltration was seen. The spleen weighed 80 Gm and appeared normal.

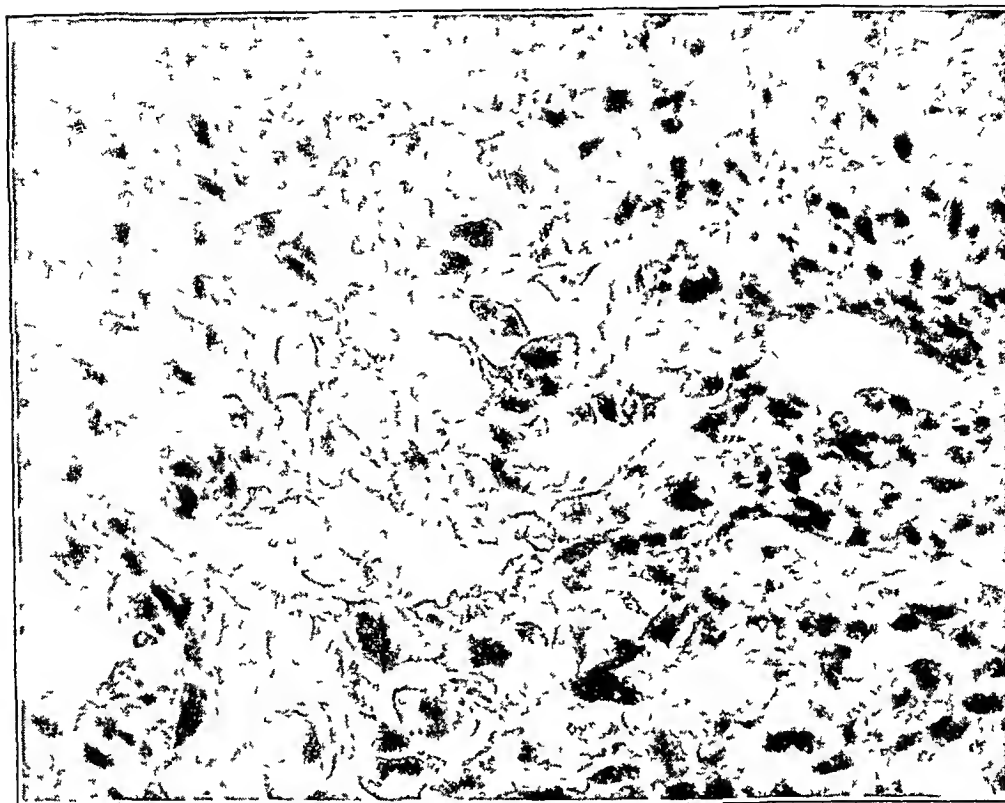


Fig 3—Chorionepithelioma, section of small nodule attached to pleura ( $\times 375$ )

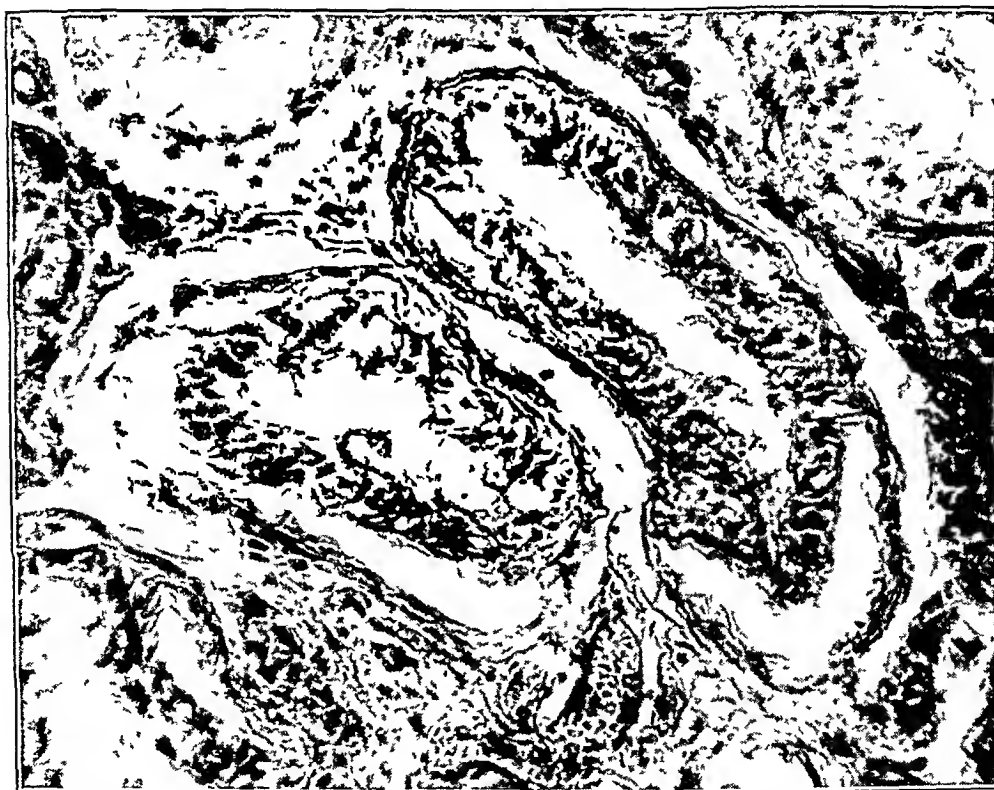


Fig 4—Section of testicle, exhibiting tubular atrophy and prominence of interstitial cells ( $\times 300$ )

About 150 cc of pink-tinged fluid was found in the left pleural cavity. The right pleural cavity was for the most part obliterated by fibrous adhesions. The right lung weighed 1,120 Gm, and the left lung weighed 1,100 Gm. Both lungs were extensively infiltrated with tumor masses of varying sizes up to 5 cm in diameter. On cross section, these masses were seen

to be variegated in nature and irregular in shape. Some of the tumor masses were firm, homogeneous and yellow, others had a mulberry-like appearance and were filled with soft cystic spaces containing dark hemorrhagic material. Many of the tumor nodules formed hemispherical masses above the visceral pleural surface and in a few areas invaded the pleura and

overlying ribs. The diaphragmatic surface of the right lung was covered with a thick white exudate, which was adherent to the diaphragm. The remaining pulmonary fields showed dense congestion and edema as well as small areas of atelectasis. The trachea and bronchi were free of exudate and obstructing masses. The mediastinal lymph nodes were not enlarged and had the appearance of normal lymphoid tissue. The heart weighed 270 Gm and presented no abnormalities.

The brain appeared somewhat edematous, and the convolutions were slightly flattened. The meninges were free of exudate. A firm dark red cystic tumor mass was seen to occupy the posterior pole of the right occipital cortex. This mass measured about 3 cm in its greatest diameter. Multiple transverse sections of the brain showed no other metastatic lesions.

*Microscopic Examination*—The retroperitoneal tumor was found to be so completely necrotic that no classification of it could be made. This necrosis may have resulted from the large amount of radiation to which the patient was subjected.

The structure of the tumor, however, was well seen in sections made of the nodules found in the large bowel, the parietal pleura, the lung, the brain and the kidneys. There was much hemorrhage and necrosis in the tumors in all these locations. The tumor cells varied considerably in size and shape. Most of these were large and pale, with large round or oval nuclei. These cells resembled the Langhans cell seen in placental tissue. Scattered among the Langhans cells were groups of syncytial cells with indefinite outline containing small hyperchromatic nuclei. In the section of the tumor removed from the descending colon, clusters of such cells were seen in the lumen of a dilated blood vessel. Sections of the lungs from portions apparently not involved in the tumor growth showed them to be somewhat more fibrous than normal and infiltrated with great numbers of small round cells and plasma cells, indicating a chronic inflammatory process, probably the result of the extensive roentgen ray therapy. No tumor growth was found in the liver, spleen, adrenal glands, or prostate.

Multiple sections of the right testis failed to reveal any tumor tissue. No spermatogenesis was present. There was moderate hyperplasia of the interstitial cells,

similar to that observed in the left testis removed at operation.

*Pathologic Diagnosis*—The lesions were diagnosed as chorionepitheliomas with their primary site probably in the retroperitoneal mass in the region of the left kidney and with metastases to the lungs, pleura, ribs, kidney, brain and large bowel.

#### SUMMARY

A case of extragenital chorionepithelioma occurring in a man was encountered.

The clinical picture the patient presented, that of gynecomastia, pain in the lumbar region, hemoptysis, loss of weight and rapid downhill course, is characteristic of tumors of embryonal urogenital origin which have widely metastasized.

The production by the tumor of large amounts of gonadotropic hormone was demonstrated by the highly positive reaction to the Friedman test with both urine and spinal fluid. The enlargement of the breasts, the absence of spermatogenesis and the interstitial hyperplasia noted in the testis are considered to have been produced by the excessive amounts of this hormone.

Intensive roentgen ray therapy over a period of five months did not alter the outcome, although it did produce some symptomatic relief and some decrease in the size of the pulmonary metastases.

Careful histologic examination of both testes revealed no tumor growth. The large retroperitoneal mass demonstrated at autopsy in the region of the left kidney was believed to represent the primary site of the chorionepithelioma.

Sections of several of the metastatic nodules revealed the presence of Langhans and syncytial cells typical of chorionic tissue.

The location of the primary growth suggests its derivation from germinal epithelium in the region of the primitive urogenital anlage.

# PLASMA QUINACRINE CONCENTRATION IN TREATMENT OF PLASMODIUM VIVAX MALARIA ACQUIRED IN THE SOUTH PACIFIC

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The development of an adequate technic for determining plasma quinacrine concentrations<sup>1</sup> has facilitated the investigation of several important phases of therapy for soldiers evacuated from the South Pacific with chronic relapsing *Plasmodium vivax* malaria. The concentrations of quinacrine in plasma attained at selected intervals as the result of oral administration of known amounts of the drug have been determined for specific dosages. Determinations were made on 6,733 specimens from 291 patients during and after treatment for four hundred and twelve attacks of malaria at Harmon General Hospital.

## METHODS

The method of Brodie and Udenfriend<sup>1</sup> was employed in the determination of the concentration of quinacrine in plasma. Plasma was used instead of whole blood because these investigators stated that variations in values in whole blood quinacrine concentrations are often reflections of changes in the number of leukocytes, since they contain a concentration several hundred times that of plasma. Shortly after the 20 to 25 cc specimens of oxalated blood were drawn, they were centrifuged at 1,500 rotations per minute for one hour. The plasma was then drawn off carefully so as to minimize contamination with white cells. Most of the determinations were made not immediately but as time permitted since it was shown that no demonstrable changes in concentration of quinacrine resulted when plasma was refrigerated for as long as seven days or kept in the frozen state for as long as four months.

In the method used quinacrine is determined by measuring its fluorescence in an acid medium. Ethylene dichloride is used to extract quinacrine as the free base from alkaline plasma. The quinacrine base is then extracted from the ethylene dichloride into lactic acid

The intensity of the fluorescence which is produced in this acid phase by ultraviolet rays of the proper wavelength is compared with that produced by a known amount of quinacrine. The measurements are made with the model 12 Coleman Electronic Photofluorometer, the B2 filter being used for the exciting light and the PC9 filter for the emitted light.

Small amounts of fluorescing quinacrine degradation products which are present in the plasma of patients undergoing therapy may accompany the quinacrine in this extraction procedure. Brodie and Udenfriend suggested the removal of these degradation products for precise work by washing the ethylene dichloride extract with 10 per cent sodium hydroxide solution. This alkaline wash was not used for our routine determinations.

*Procedure*—1 Ten cubic centimeters of plasma and 3 cc of phosphate buffer at pH 8 were extracted with 30 cc of ethylene dichloride.

2 A 20 cc portion of the ethylene dichloride layer was extracted with 1 cc of water and 10 cc of lactic acid U S P XII (Mallinckrodt).

3 Standards and blanks were prepared in duplicate by additions of 1 cc portions of quinacrine solutions of known concentrations to 10 cc portions of lactic acid, each being shaken with 20 cc of ethylene dichloride.

4 The intensity of fluorescence produced in the lactic acid phase of the plasma extract was compared with that of the standards, and the concentration in micrograms of quinacrine base per liter of plasma was calculated. One gram of quinacrine dihydrochloride dihydrate is equivalent to 0.78 Gm of quinacrine base. The results presented in all tables and figures are reported as quinacrine base.

*Reliability of the Method*—The precision of the results obtained by the method employed may be gaged by the data presented in table 1. An average blank value corresponding to 3 micrograms of quinacrine per liter of plasma was obtained. The blanks were not subtracted from the values obtained. When known amounts of quinacrine were added to 5 or 10 cc por-

<sup>1</sup> Brodie, B B and Udenfriend, S. The Estimation of Atabrine in Biological Fluid and Tissues, *J Biol Chem* **151** 299-317 (Nov) 1943.

tions of plasma, the proportions recovered were usually approximately 96 per cent, although on an occasional day all results were either slightly high or slightly low. The average recoveries, the ranges of values and individual results obtained in two consecutive series of such recovery experiments are shown in table 1.

TABLE 1—Recoveries of Quinacrine Added to Plasma

Number of Tests	Micrograms Quinacrine Added to 5 or 10 Cc Plasma	Average Recovery	Range
49	0	3 micrograms per liter	0 to 4 micrograms per liter
16	0.25	96%	88 to 106%
30	0.50	96%	86 to 110%
49	1.00	96%	82 to 104%

Results Obtained in Two Consecutive Series of Determinations								
Micrograms of Quinacrine Added to 5 Cc Plasma	Micrograms of Quinacrine Recovered							
	Series 1				Series 2			
0	0	0	0.01		0.02	0.02	0.015	
0.25	0.22	0.23	0.24	0.24	0.24	0.26	0.26	0.24
0.50	0.48	0.48	0.47	0.48	0.51	0.50	0.50	
1.00	1.00	0.98	0.98	0.98	1.00	1.00	0.98	0.96

## TREATMENT

The patients in this study all received quinacrine dihydrochloride dihydrate (hereafter referred to under treatment as quinacrine hydrochloride) and were divided into four groups. Treatment for patients in groups I, II, and III was begun at the first regular time for drug administration, that is, at meal time or at midnight, after their admission to the ward with an attack of malaria, which was arbitrarily defined as temperature over 100 F and a smear positive for Plasmodia. The approximate times of the meals were 7:30 a.m., 11:30 a.m. and 5 p.m.

**Group I**—Standard treatment. Quinacrine hydrochloride, 0.2 Gm, was given orally for five doses with meals and at midnight, totaling 1 Gm in twenty-four hours of treatment. This was followed by 0.1 Gm three times daily with meals until a total of 2.8 Gm had been given.

**Group II**—A total of 2.8 Gm of quinacrine hydrochloride was given as in group I, followed by a twenty-four hour rest period, then 0.01 Gm of pamaquine naphthoate three times daily for three days followed by 0.1 Gm of quinacrine hydrochloride six days per week through the sixtieth day from the initial day of treatment.

**Group III**—A total of 2.8 Gm of quinacrine hydrochloride was given as in group I, followed by 0.1 Gm of quinacrine hydrochloride six days per week from the eighth through the sixtieth day from the initial day of treatment.

**Group IV**—The amount of quinacrine hydrochloride given by mouth was 0.4 Gm at 9 a.m. followed by 0.2 Gm at 4:30 p.m. and at 1 a.m. Thereafter 0.2 Gm was given at 9 a.m. and at 9 p.m. for six days. The total was 3.2 Gm.

## RESULTS

**Fasting Plasma Concentrations** (Groups I, II and III)—The 104 patients studied included 54 patients of group I and 50 patients of groups II and III. The concentration of quinacrine in plasma obtained before breakfast was determined for all these patients for eight days while undergoing similar therapy. Thereafter the fasting levels were determined for only the 54 patients of group I on the ninth and tenth days, every other day for ten more days and again on the twenty-eighth day.

The average fasting plasma quinacrine concentrations obtained on each full day of treatment of the 104 patients as well as the average values for each treatment group are shown in table 2. It can be seen that with the exception of those obtained on the morning of the first day of treatment the fasting values were but little affected by the variation of the hour at which treatment had been instituted because

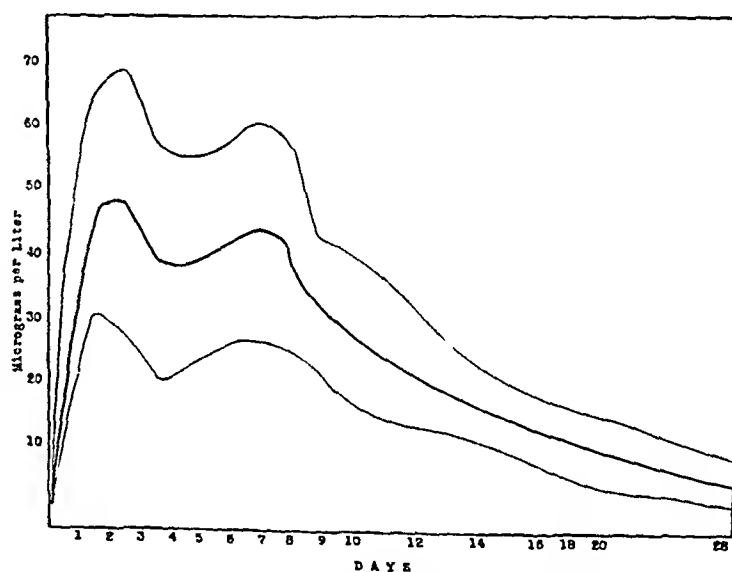


Fig 1—Fasting plasma quinacrine concentrations in 104 patients for eight days and in 54 patients thereafter (2.8 Gm of quinacrine hydrochloride in one week). The heavy line indicates average values. Fine lines indicate 1 standard deviation (includes approximately two thirds of all values).

the total amounts of drug received by a given time were practically identical in each case.

The average values, however, do not necessarily represent the values which would be attained by any given person receiving a similar type of therapy. There was much variation between the results obtained on different persons, although most of the curves were characterized by a rapid rise, a dip and then a slower rise until treatment was discontinued. The extent of these variations may be gaged from chart 1, in which are shown the standard deviations from the average values. The area between the upper and lower curves includes approximately two thirds of all values. One

third of the values were either above or below these limits, and isolated values of as high as 120 and as low as 5 micrograms per liter were obtained during the week of treatment

After the administration of quinacrine hydrochloride was discontinued, the plasma concen-

per liter, two and four hours after dinner, 66 and 113 micrograms per liter, and two and four hours after supper, 12 and 8 micrograms per liter The average daily changes at the specified times are shown in chart 2, in which these values are superimposed on the average fasting curve for the 104 men The average patterns on each day are similar, with moderately elevated values being found early in the day and with peak values being found later in the day The individual curves again showed considerable irregularity, with an occasional postprandial level being slightly below the fasting level

*Plasma Quinacrine Concentrations in Groups 2 and 3*—All specimens from the 215 patients in these two groups were obtained at approximately four hours after breakfast The total amount of quinacrine hydrochloride given to the patients in group III was approximately 73 Gm, while those in group II received 04 Gm less The average values obtained are

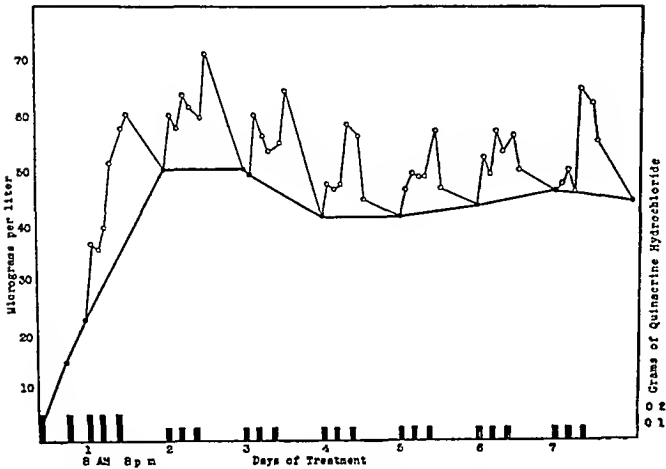


Fig 2—Diurnal variation of plasma quinacrine concentrations in 104 patients given 28 Gm of quinacrine hydrochloride

TABLE 2—Average Fasting Plasma Quinacrine Concentrations with Reference to Dosage

Day of Attack		Full Days of Treatment															
Time of First Treatment	Per Cent of Pa-tients	1		2		3		4		5		6		7		8	
		Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm	Fast-ing Value*	Drug,† Gm
7 30 a m	6	08	54	12	65	15	53	18	47	21	45	24	49	27	56	28	33
11 30 a m	22	06	35	11	53	14	49	17	44	20	44	23	48	26	52	28	48
5 00 p m	54	04	21	10	50	13	48	16	39	19	40	22	42	25	44	28	47
12 midnight	18	02	15	10	52	13	56	16	43	19	44	22	45	25	51	28	54
Average		04	25	10	52	13	50	16	41	19	42	22	44	25	48	28	48

\* Micrograms per liter  
† Total drug received by 12 midnight

trations fell slowly, so that by four weeks after the attack the average value was 8 micrograms per liter, with a range of 2 to 21 micrograms per liter From the eighth to the ninth day the average concentration decreased by 21 per cent, and from then until the eighteenth day the daily decreases were approximately 10 per cent During the next ten days the levels decreased more slowly

*Diurnal Variations of Plasma Quinacrine Concentration in 104 Patients*—A simultaneous study of the diurnal variations of the plasma concentrations during the week of treatment was made by obtaining blood specimens from six groups of approximately 15 patients each at two or at four hours after administration of the drug at breakfast, dinner and supper respectively in addition to the fasting specimens

The average rises in values above the individual daily fasting levels on the second through the seventh days were as follows two and four hours after breakfast, 23 and 68 micrograms

shown in chart 3 Again there were considerable individual differences, as shown by the standard deviations After the dosage of the

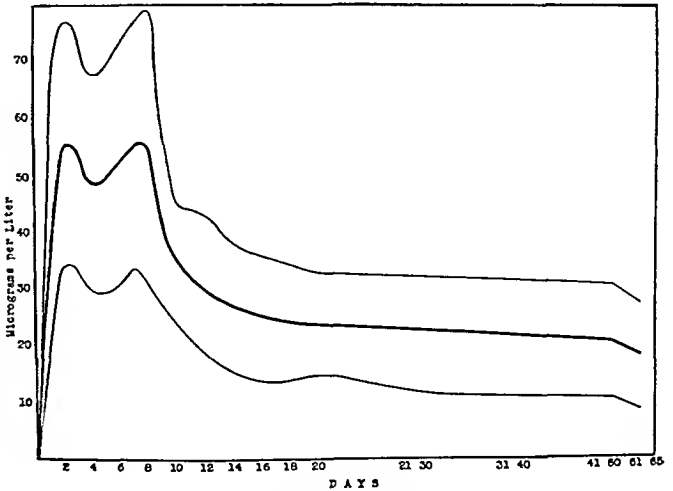


Fig 3—Plasma quinacrine concentrations at 11 a.m of 226 patients who were given 28 Gm of quinacrine hydrochloride in one week The heavy line indicates average values for hours after administration of 01 Gm Fine lines indicate 1 standard deviation (includes approximately two thirds of all values)

drug was reduced, the levels at first dropped rather sharply and then gradually leveled off to a concentration of approximately 23 micrograms per liter. The rates of fall of the con-

TABLE 3—Elevations Above Fasting Levels Four Hours After Administration of Quinacrine Hydrochloride with Breakfast

	Days						
	First	Second	Third	Fourth	Fifth	Sixth	Seventh
	Micro gram per Liter	Micro gram per Liter	Micro gram per Liter	Micro gram per Liter	Micro gram per Liter	Micro gram per Liter	Micro gram per Liter
A	9	5	4	7	8	8	8
B	13	7	10	6	9	6	4

A = elevation of 11 a m concentrations of 215 patients above fasting concentrations of 104 patients on the same type of therapy

B = Elevations of 11 a m concentrations of 15 patients above their own fasting values on the same days

centrations of groups II and III did not differ significantly. These daily 11 a m levels during the week of active treatment exceeded the

gradually exceeded the others until by the morning of the eighth day the two figures were 48 and 63 micrograms per liter.

When the administration of the drug was stopped, the levels decreased approximately 20 per cent per day for two days and then at a rate of approximately 10 per cent per day until the eighteenth day, at which time the levels were practically identical with those obtained with group 1 at this time (15 micrograms per liter).

*Plasma Quinacrine Concentrations in Successive Attacks*—Plasma quinacrine concentrations were determined in successive attacks in 71 patients to observe whether the levels were similar on a repetition of the same dosage (2.8 Gm in one week). In some instances curves were obtained for three successive attacks. Many of the curves obtained in two or even three attacks resembled each other closely, but there were also instances in which wide differences existed. Chart 5 is an example of two successive curves for 1 patient, with both representing levels considerably higher than the average for group II.

TABLE 4—Average Fasting Plasma Quinacrine Levels of the Groups Receiving 2.8 Gm and 3.2 Gm Respectively

Group	Attack  Drug by End of Day, Gm	Days of Treatment															
		1		2		3		4		5		6		7		8	
		Microgram per Liter	Drug by End of Day, Gm	Level*	Gm †	Level*	Gm †	Level*	Gm †	Level*	Gm †	Level*	Gm †	Level*	Gm †	Level*	
3.2 Gm group	0	3	0.8	36	1.2	43	1.6	46	2.0	49	2.4	51	2.8	61	3.2	63	
2.8 Gm group	0.4	25	1.0	51	1.3	51	1.6	42	1.9	42	2.2	44	2.5	47	2.8	48	

\* Level refers to micrograms per liter  
† Grams of drug received by end of day

average fasting levels of the 104 patients (in chart 1) by the amounts shown in table 3 and approximated the values found for the smaller group of 15 patients previously studied at 11 a m.

*Plasma Quinacrine Concentrations in Group 4*—The specimens of plasma were obtained from these patients before the morning doses of drug (twelve hours after last dose), and, in addition, on days 1, 2 and 7 specimens were obtained at 2 p m (five hours after the morning dose). The average concentrations found at these times are shown in chart 4, in which the solid line represents the "fasting" values and the broken lines connect the three five-hour values with the preceding and the following average fasting values. The shape of this fasting curve differs from those of the other groups because the schedules of doses were different. The levels on the first three days tended to be lower because less drug had been given, but by the fourth day the same amount of drug had been received by each group and the fasting concentrations were nearly the same. After this time however the values in group IV

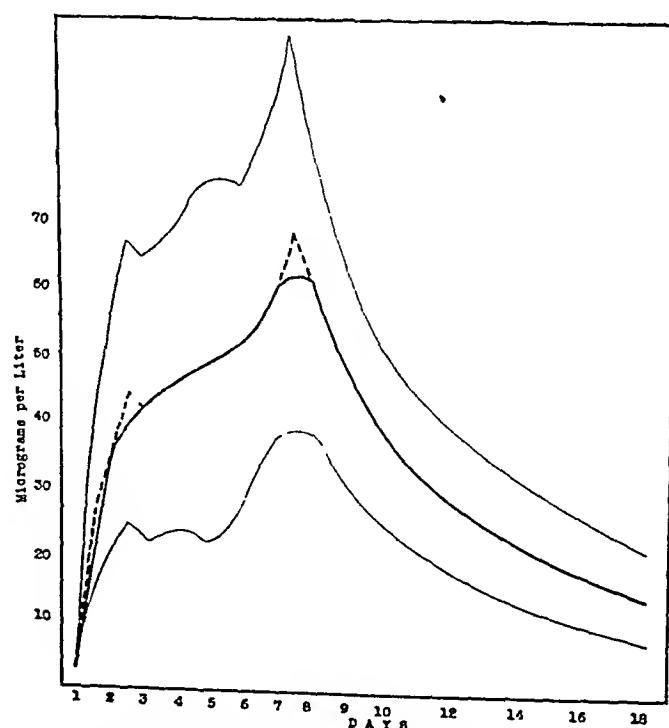


Fig 4—Plasma quinacrine concentrations of 35 patients who were given 3.2 Gm of quinacrine hydrochloride in one week. The heavy line indicates average fasting values. The broken line indicates five hours after administration of 0.2 Gm. Fine lines indicate 1 standard deviation (includes approximately two thirds of all values).

treatment In contrast is chart 6, showing three successive curves for 1 patient in whom the levels were consistently below the average for group I and II treatment Another variant is seen in chart 7, in a patient who broke through suppressive treatment with an attack of malaria after measles had developed The

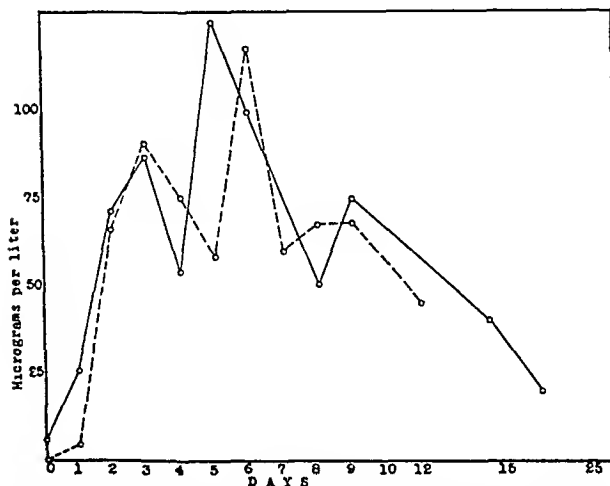


Fig 5—Plasma quinacrine concentrations in successive attacks (high levels) The continuous line indicates the nineteenth attack and the broken line the twentieth attack

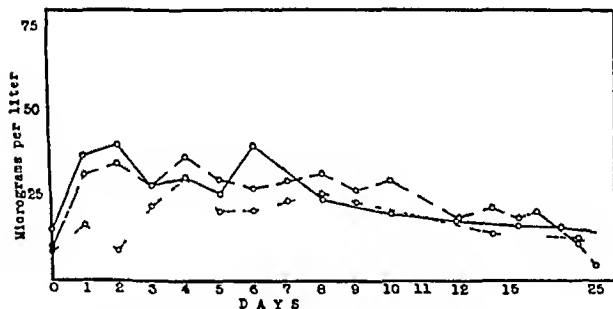


Fig 6—Plasma quinacrine concentrations in successive attacks (low levels) The eighteenth attack was a breakthrough while the patient was taking 0.1 Gm of quinacrine hydrochloride daily Long dashes indicate the sixteenth attack, short dashes, the seventeenth attack, and the continuous line, the eighteenth attack

plasma concentration during treatment for this attack was considerably higher than in two previous attacks because of the start of treatment with the level already at 35 micrograms per liter

#### COMMENT

The oral administration of quinacrine hydrochloride as outlined for groups I, II and III was followed by prompt disappearance of parasites from the blood, 90 per cent of the smears in two hundred and thirty-four attacks were negative within thirty-two to forty-eight hours after initiation of treatment There was also prompt subsidence of fever, 66 per cent of the patients in three hundred and thirteen attacks

had normal temperatures on the second day after initiation of treatment and 94 per cent by the fifth day Symptoms were readily relieved, and by seventy-two hours after the beginning of treatment the patients were usually able to leave the ward for recreational purposes

The reliability of the method for determining plasma quinacrine concentrations is apparent from table 1, in which it is shown that the average recovery is 96 per cent when amounts as small as 0.25 microgram of quinacrine hydrochloride are added to 5 or 10 cc of plasma The values obtained for the concentrations in the plasma of patients undergoing therapy are probably slightly higher than the actual concentrations because of the inclusion of small amounts of fluorescent degradation products of quinacrine While the average values for the fasting and the postprandial curves gave a rather

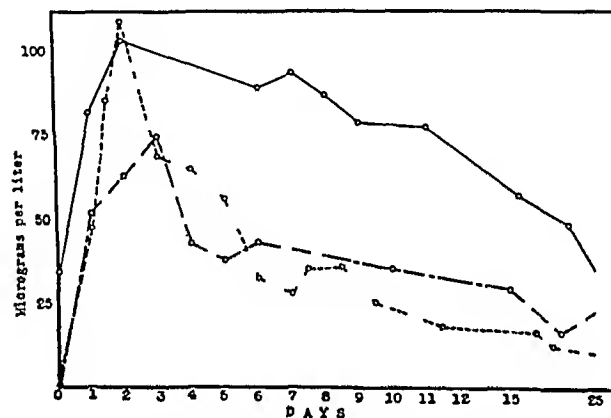


Fig 7—Plasma quinacrine concentrations in successive attacks (breakthrough during measles) Measles developed in this patient thirty-five days after completion of treatment with quinacrine hydrochloride, 2.8 Gm, and while he was taking 0.1 Gm of quinacrine hydrochloride daily A breakthrough with another attack of malaria occurred at this time, while the plasma quinacrine concentration was 25 micrograms per liter Short dashes indicate the seventh attack, long dashes, the ninth attack, and the continuous line the tenth attack

constant pattern, it is to be emphasized that there were many individual variations When group I treatment was discontinued, the levels fell rather slowly, but when this was followed by 0.1 Gm of quinacrine hydrochloride six days per week the levels fell more slowly and did not fall below a concentration of approximately 23 micrograms per liter At this average concentration there was only an occasional breakthrough with another attack

The clinical effectiveness of the administration of 2.8 Gm of quinacrine hydrochloride in one week is obvious, but it may also be true that a smaller amount might be effective For example, while this dosage gives average fasting levels from the second to the eighth days

of 41 to 52 micrograms per liter, a lower level might conceivably be adequate. We have had no experience with a lower dosage, although some of our patients in whom the concentrations were lower than the average had satisfactorily prompt relief from symptoms.

#### SUMMARY AND CONCLUSIONS

The concentration of quinacrine was determined in 6,733 specimens of plasma obtained from 291 patients both during and after four hundred and twelve attacks of *P. vivax* malaria of South Pacific origin. The standard treatment was the oral administration of 2.8 Gm of quinacrine hydrochloride in approximately seven days. For 33 patients, however, the amount was 3.2 Gm.

The range of the daily average fasting values on the standard 2.8 Gm treatment from the second through the eighth day was 41 to 52 micrograms per liter, while the concentrations of specimens taken four hours after the first daily dose of drug were 49 to 57 micrograms per liter. After the administration of the drug was discontinued, the levels decreased slowly, so that by four weeks after the beginning of treatment the average fasting concentration was 8

micrograms per liter. Individual curves frequently differed from the average pattern.

The average plasma concentrations at two and four hours after the administration of 0.1 Gm of quinacrine hydrochloride with each meal varied from 2.3 to 12 and 6.8 to 11.3 micrograms per liter above the corresponding fasting levels.

During the period of suppressive treatment in the patients followed through the sixtieth day from the start of treatment (2.8 Gm), the levels dropped slowly to an average concentration of 2.3 micrograms per liter.

The range of the daily average fasting quinacrine hydrochloride concentrations on the 3.2 Gm treatment from the second through the eighth day was 36 to 63 micrograms per liter. When treatment was discontinued, the levels fell slowly, so that by the eighteenth day after treatment was started the average concentration was approximately that attained by the standard 2.8 Gm group (15 micrograms per liter).

When a fasting plasma quinacrine concentration of approximately 45 micrograms per liter was attained within twenty-four hours and maintained, the symptoms of the attacks were usually abolished within seventy-two to ninety-six hours after the start of treatment.

# Progress in Internal Medicine

## BLOOD

### A REVIEW OF THE RECENT LITERATURE

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AND MURIEL C MEYERS, MD

ANN ARBOR, MICH

(Continued from Page 254)

#### IRON METABOLISM AND EXPERIMENTAL ANEMIA

Powell<sup>51</sup> determined the serum iron values for a series of 70 normal persons and for patients with various types of anemia. Mean values of 143 micrograms per hundred cubic centimeters for men and 117 micrograms for women were obtained. Evidence was obtained showing that the serum iron level falls during the menstrual period in normal women. The serum iron level was generally low in patients with hypochromic anemias, but after the beginning of treatment values as high as 400 micrograms per hundred cubic centimeters were found in many cases. In 2 patients a satisfactory hemoglobin response to iron therapy was obtained only after simultaneous administration of ascorbic acid. The author is inclined to attribute the benefit derived from the use of ascorbic acid to the reduction of ferric iron and its maintenance in the ferrous state during its passage into the upper part of the small intestine. One of the patients studied had hypochromic anemia refractory to iron therapy even when ascorbic acid was added, and the low serum iron values persisted through the period of treatment. The cause of this failure to absorb iron was not determined. The lowest value for serum iron, 15 micrograms per hundred cubic centimeters, was obtained for a patient with scurvy. High serum iron levels were found in patients with aplastic anemia and pernicious anemia. After the commencement of liver therapy for patients with the latter disease, levels as low as 30 micrograms were found. The values for serum iron in patients with hemolytic anemia were not significantly raised, and it was thought that in these circumstances breakdown and synthesis of hemoglobin were proceeding at approximately equivalent rates.

Footnotes 49 and 50 have been renumbered and appear elsewhere in this review.

<sup>51</sup> Powell, J F. Serum-Iron in Health and Disease, *Quart J Med* **13** 19, 1944.

Moore and his collaborators<sup>52</sup> using the radioactive isotope, reinvestigated the absorption of ferrous and ferric iron by human subjects and by dogs. Among physicians and clinical investigators there is agreement that patients with hypochromic anemia require from four to six times the quantity of iron in the form of a soluble ferric salt as that contained in a soluble ferrous preparation which must be given to produce a comparable therapeutic effect. Studies on the absorption of iron in human beings likewise have regularly shown that the bivalent form of the metal is more completely assimilated than is the trivalent. In investigations on animals less consistent results have been obtained, and some investigators have concluded that there is no difference in the degrees to which ferrous and ferric salts are absorbed. Six normal dogs were given 1 mg per kilogram of body weight of either ferric or ferrous radioactive iron, the latter being reduced from the trivalent state by ascorbic acid. The appearance of the labeled element as newly synthesized hemoglobin in the peripheral blood was determined as a measure of the amount absorbed. In about half of the experiments the two forms of the iron were absorbed equally well, while in the remainder the ferrous form was assimilated better.

Similar doses of radioactive iron were given to 4 anemic dogs whose iron reserves had been depleted by repeated bleeding. A greater proportion of the total iron was absorbed by these animals than by those in the normal group, and there was approximately equal assimilation of the two valence forms.

Ferrous and ferric iron in test doses of 1, 2 and 4 mg per kilogram of body weight were given to 8 different men with normal blood values. In each case more ferrous than ferric

<sup>52</sup> Moore, C V, Dubach, R, Minnich, V, and Roberts, H K. Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs, *J Clin Investigation* **23** 755, 1944.

iron was absorbed. The ratio of the amount of the bivalent form assimilated to that of the trivalent form assimilated varied from  $1\frac{1}{2}$  to 10. Similar studies were made on 5 patients with severe hypochromic microcytic anemia. The bivalent form was absorbed from two to fifteen times as well as the ferric form. The percentage assimilated was greater with the small doses than with the large, and the iron-deficient subjects tended to absorb a greater proportion of the iron than did the men with normal blood values.

Boyd, Hitsman and Perry<sup>53</sup> investigated the storage and elimination of iron compounds injected intramuscularly into albino rats. Of the iron injected none was lost or excreted in the feces, and only 1 to 2 per cent was excreted in the urine. About two thirds of the injected iron was stored in the liver, and smaller amounts were deposited in the walls of the intestines, the bones, the muscles and elsewhere.

Hahn and his collaborators<sup>54</sup> studied the absorption of red blood cells from the peritoneal cavity of dogs. Red blood cells labeled by radioactive iron in their hemoglobin were injected into the peritoneal cavity of normal dogs. Between 20 per cent and 100 per cent of the cells were found to be circulating in the blood within twenty-four hours. Anemic dogs absorb red cells in this manner a little less readily, and dogs depleted of both hemoglobin and protein absorb them even less readily. Although transit of the red cells from the peritoneal cavity to the circulation is surprisingly rapid, the rate varies widely in different dogs and in the same dog at different times.

An attempt to mobilize the iron in a patient with hemochromatosis by the administration of various chemicals was made by Fishback.<sup>55</sup> Over an experimental period of one week each the patient was given sodium thiosulfate, ammonium chloride and sodium bicarbonate by mouth and sodium thiosulfate intravenously while a careful chemical check of the iron balance was maintained. None of the compounds administered was found to have a definitely significant effect in mobilizing iron or in producing a negative iron balance.

<sup>53</sup> Boyd, E. M., Hitsman, J. S., and Perry, W. F. The Storage and Elimination of Iron Compounds Injected Intramuscularly into Albino Rats, *Rev. canad. de biol.* **3**: 294, 1944.

<sup>54</sup> Hahn, P. F., and others. Peritoneal Absorption. Red Cells Labeled by Radio-Iron Hemoglobin Move Promptly from Peritoneal Cavity into the Circulation. *J. Exper. Med.* **80**: 77, 1944.

<sup>55</sup> Fishback, H. R. On the Mobilization of Iron in Hemochromatosis with Administration of Various Chemicals, *J. Lab. & Clin. Med.* **29**: 742, 1944.

Lucia and Marasse<sup>56</sup> reviewed at length the rather large volume of work done in evaluating the effect of the central nervous system on hemopoiesis. The authors concluded that a relation between the hypothalamus and erythropoiesis or between localized lesions or other diseases of the central nervous system and erythropoiesis has not been convincingly demonstrated.

Brown, Hayward, Powell and Witts<sup>57</sup> studied the rate of destruction of transfused erythrocytes by the Ashby method of differential agglutination. In 6 cases of idiopathic hypochromic anemia a nearly constant linear curve of destruction occurred. The transfused erythrocytes survived on the average fifty days. In 3 cases in which excessive hemolysis was apparent clinically, 1 that of a patient with a metastatic neoplasm and the other 2 of patients with acquired hemolytic anemias, the rate of hemolysis of the transfused red blood cells was nearly twice as rapid. The plotted values in the latter cases were curvilinear, with the most rapid hemolysis occurring during the first week. In 7 patients with anemia due to infection and in 12 other patients, single patients with such conditions as thyrotoxicosis, chronic nephritis and pernicious anemia under treatment with liver extract, variably accelerated rates of destruction of erythrocytes were found. The plotted curves were both linear and curvilinear in type. In most patients with acute anemia an unduly rapid rate of red cell destruction was found, while in patients with chronic anemia the rate of destruction was normal.

Higgins<sup>58</sup> designed a number of animal experiments using young male rats to test the value of vitamin B<sub>12</sub> (folic acid) in correcting or preventing the anemia resulting from the administration of promin (sodium p, p'-diaminodiphenylsulfone-N,N'-dioxetose sulfonate) and promizole (4,2'-diaminodiphenyl-5'-thiazole-sulfone). The rats were fed a diet high in purified carbohydrate supplemented with thiamine, riboflavin, pyridoxine, calcium pantothenate, nicotinic acid and choline chloride. The addition of either of the two sulfone compounds to this diet had been shown to induce a hypochromic,

<sup>56</sup> Lucia, S. P., and Marasse, H. F. The Central Nervous System and Hematopoiesis, *J. Nerv. & Ment. Dis.* **99**: 734, 1944.

<sup>57</sup> Brown, G. M., Hayward, O. C., Powell, E. O., and Witts, L. J. Destruction of Transfused Erythrocytes in Anaemia, *J. Path. & Bact.* **56**: 81, 1944.

<sup>58</sup> Higgins, G. M. The Influence of Vitamin B<sub>12</sub> Concentrate (Folic Acid) on Experimental Anemia in the Rat, *Proc. Staff Meet., Mayo Clin.* **19**: 329, 1944.

although macrocytic, anemia in the rats. In 1 experiment, 80 micrograms of vitamin B<sub>12</sub> per day was given orally to a group of rats receiving 50 mg of promin daily. In another experiment, the anemia was first induced by giving promin in the same amount daily for two weeks. Vitamin B<sub>12</sub> was then given orally to part of this group of animals for two weeks, while the remaining animals continued to receive promin but not the vitamin. A third experiment was conducted after the pattern of the second, with the anemia being first induced by giving promizole, 25 mg per day. The author's findings appeared to indicate that under the experimental conditions set up vitamin B<sub>12</sub> in daily amounts of 80 micrograms orally exerted a pronounced antianemic effect on the animals in which the anemia had been previously induced.

Michaud, Maass, Ruegamer and Elvehjem<sup>59</sup> studied regeneration of hemoglobin in dogs maintained on a purified sucrose-casein-synthetic vitamin ration to which succinylsulfathiazole in amounts varying from 0.5 to 4 per cent had been added. They attempted in this way to modify the intestinal flora and to cause a deficiency of factors possibly synthesized in the digestive tract. It had been found that dietary levels as low as 0.5 per cent of succinylsulfathiazole were injurious to rats under similar conditions. The hemoglobin content per hundred cubic centimeters of circulating blood, total hemoglobin number of red blood cells, mean cell volume, food consumption, growth increase and the general state of health were the factors taken into consideration. In dogs they could find no difference between the animals receiving the drug and those serving as controls.

#### NUTRITION AND ANEMIA

Some of the fundamental relations between the plasma proteins, cell proteins and the protein constituents of hemoglobin are reviewed by Whipple and Madden<sup>60</sup>. In recent years a large number of observations have been made in their laboratory to show that a dynamic equilibrium exists between plasma protein and cell protein which enables protein to flow in either direction, depending on the conditions of the moment. All the nitrogen requirements of dogs, for instance, can be supplied by dog plasma given by vein.

<sup>59</sup> Michaud, L., Maass, A. R., Ruegamer, W. R., and Elvehjem, C. A. Hemoglobin Regeneration in Dogs Receiving a Purified Ration Plus Succinylsulfathiazole, *Proc Soc Exper Biol & Med* **56** 148, 1944.

<sup>60</sup> Whipple, G. H., and Madden, S. C. Hemoglobin, Plasma Protein and Cell Protein. Their Interchange and Construction in Emergencies, *Medicine* **23** 215, 1944.

With large injections of plasma, hyperproteinemia did not develop and the albumin-globulin ratio was not altered. Other experiments showed that protein stored as cell protein was available for the manufacture of hemoglobin and plasma protein in dogs rendered hypoproteinemic. Some observations indicate that a plasma-depleted dog on a liberal protein diet can produce more new plasma protein, 70 Gm or more per week, than a standardized anemic dog can produce hemoglobin, 70 Gm or less per week. The body is able to make new hemoglobin and plasma protein out of materials contained in digests made from serum. Dogs are able to manufacture abundant plasma protein derived at least in part from dog or sheep hemoglobin when this is injected intraperitoneally. Casein digests administered in this way are also effective. Twenty-five to 40 Gm of new hemoglobin and plasma protein may be produced from 100 Gm of digest.

Cartwright, Wintrobe and Humphreys<sup>61</sup> report further studies on the anemia in swine due to pyridoxine deficiency. Deficiency of this vitamin had been shown to result in nutritional microcytic anemia in both dogs and pigs, an anemia which did not respond to administration of iron or copper but which was relieved by synthetic pyridoxine. Convulsions, ataxia, degeneration of the peripheral nerves and presence of hemosiderin in the spleen, liver and bone marrow had occurred in the experimental animals. An elevation of the plasma iron was found in animals deficient in pyridoxine, and a green pigment-producing substance was present in the urine which was found to be xanthurenic acid, a product derived from tryptophan metabolism.

The authors studied the effects of pyridoxine deficiency on the blood of swine in comparison to those of iron deficiency and of phenylhydrazine hemolytic anemia with iron controls. The major conclusions were as follows. An increased rate of hemolysis does not occur in pyridoxine deficiency. By restricting the dietary intake of iron in pyridoxine-deficient animals, hemosiderosis could be prevented and the serum iron maintained at the low level seen in iron deficiency. The ataxia, convulsions, neurologic lesions and fatty liver characteristic of animals with pyridoxine deficiency were not altered by limiting the iron intake to produce a combined deficiency of both iron and pyridoxine. The

<sup>61</sup> Cartwright, G. E., Wintrobe, M. M., and Humphreys, S. Studies on Anemia in Swine Due to Pyridoxine Deficiency, Together with Data on Phenylhydrazine Anemia, *J Biol Chem* **153** 171, 1944.

urinary excretion of iron in pyridoxine-deficient animals was not altered and remained insignificant. The increased amount of iron found in the blood serum was found to exist in the trivalent state. The administration of chlorophyll, purified liver extract, tryptophan, corn oil, crude hemoglobin, hemin and iron ascorbate were all ineffective in stimulating blood formation in this deficiency state. The authors regard the ferremia and hemosiderosis as being due to the continued absorption or decreased excretion of iron at a time when its utilization for hemoglobin formation is at a minimum and when the body tissues are abundantly supplied with iron.

Wintrobe, Follis, Alcayaga, Paulson and Humphreys<sup>62</sup> studied the effects of pantothenic acid deficiency in swine by maintaining the animals on a purified diet supplemented by all the known crystalline B vitamins other than pantothenic acid. With such a diet young pigs manifested signs of deficiency much sooner than did similar pigs receiving calcium pantothenate but lacking any one of the following: thiamine, riboflavin, nicotinic acid, pyridoxine or choline. Growth was quickly inhibited and diarrhea was severe and was accompanied with extensive pathologic changes in the colon. Sudden collapse occurred and ended fatally. Less pronounced effects of pantothenic acid deficiency in pigs were loss of hair, reddening of the skin, excessive nasal secretion, changes in the tongue and degenerative changes in the nervous system associated with the development of noticeable abnormalities in gait.

A severe anemia such as that which occurs in pyridoxine deficiency did not develop in the pantothenic acid-deficient pigs. A moderate normocytic anemia was noted in 13 out of 18 pigs. In 7 the volume of packed red cells ranged between 35 and 40 cc per hundred cubic centimeters of blood, and in the remainder the volume of packed red cells ranged between 24 and 33 cc (the normal range in pigs being 41.5 to 51.5 cc). Two animals were treated with calcium pantothenate, and the anemia became less pronounced.

Maass and his collaborators<sup>63</sup> studied the relation of thiamine to blood regeneration in growing and in adult dogs. The animals were maintained on a purified diet supplemented with all

the crystalline vitamin B fractions except thiamine and rendered anemic by repeated phlebotomy. No specific effect of the thiamine deficiency on the capacity for blood regeneration was found.

Bass<sup>28</sup> reports on 2 infants with nutritional anemias. In a 6 month old infant, weakness and pallor developed after an infection of the upper respiratory tract. The hemoglobin content of the blood was found to be 17 per cent and the red cell count 920,000. The infant was admitted to the hospital and given blood transfusions, iron and large doses of vitamins. There was, however, a progressive fall in the blood level during an observation period of four weeks. Injections of liver extract were then started, and the infant made a complete and uneventful recovery.

Another infant, 5 months old, had become severely allergic to cow's milk early in life and was given a goat's milk formula with vitamin B and C supplements. Anemia, with a hemoglobin content of 36 per cent and a red blood cell count of 1,630,000, was present at the age of 2½ months. This was treated by several small transfusions and by the addition of an iron preparation to the diet. The feeding problem and the severe eczema became worse, and the infant's condition became critical. The child was given a formula containing the amino acids derived from hydrolyzed casein with vitamin and iron supplements as before. In less than a month the cutaneous lesions had cleared and the blood levels were being maintained satisfactorily. It was the author's opinion that the hematologic improvement resulted from the more adequate protein nutrition provided by the amino acids.

Davidson and Donaldson<sup>64</sup> found mild degrees of anemia relatively common among English school children and investigated its response to treatment with iron and ascorbic acid. They found that the anemia responded well to the administration of as little as 15 grains (0.97 Gm) of ferrous sulfate a week. A supplement of 25 mg of ascorbic acid daily in addition had no effect in raising the hemoglobin level.

Pijoan and Elkin<sup>65</sup> investigated the cause of anemia among Shoshone Indian infants fed for prolonged periods on an exclusive milk diet. It was the tribal custom to give the infants nothing but breast milk until they were 1 or 2

62 Wintrobe, M. M., Follis, R. H., Alcayaga, R., Paulson, M., and Humphreys, S. Pantothenic Acid Deficiency in Swine, with Particular Reference to the Effects on Growth and on the Alimentary Tract, *Bull. Johns Hopkins Hosp.* **73**: 313, 1943.

63 Maass, A. R., Michaud, L., and others. The Relation of Thiamine to Blood Regeneration, *Arch. Biochem.* **4**: 105, 1944.

64 Davidson, L. S. P., and Donaldson, G. M. M. Treatment of Anemia in School-Children with Iron and Ascorbic Acid, *Brit. M. J.* **1**: 76, 1944.

65 Pijoan, M., and Elkin, C. A. Secondary Anemia, Due to Prolonged and Exclusive Milk Feeding Among Shoshone Indian Infants, *J. Nutrition* **27**: 67, 1944.

years of age and could eat the unmodified adult food. The breast milk from nursing mothers was found to contain but 1.7 to 1.8 mg. of iron per liter, an amount low enough to account for the prevailing anemia due to iron deficiency.

Civeira Otermin<sup>66</sup> studied the blood changes, particularly regarding the cellular elements and bone marrow, in 40 cases of chronic starvation with edema. In these cases the number of platelets in the peripheral blood was found to be decreased, the counts averaging 187,000. The average white blood cell count was 6,000, with a relative and absolute lymphocytosis and neutropenia. The studies of the bone marrow showed an increase in the number of megakaryoblasts with the erythrocyte-granulocyte ratio disturbed by an increase in the granulocytic elements. A certain degree of arrest of maturation in both series resulting in an increase in the less differentiated elements was observed. There was no alteration in the megakaryocytes.

According to Weder,<sup>67</sup> the Plummer-Vinson syndrome has been diagnosed very rarely in Switzerland, possibly because the syndrome has not been recognized. He reported on 4 women with the syndrome, whose ages ranged from 31 to 51 years. In the majority of the patients there were soreness and burning of the mouth and tongue, painful recurrent fissures at the angles of the mouth, difficulty in swallowing solid and even liquid foods and symptoms of anemia. All the patients had smooth tongues with atrophic papillae, perleche and severe hypochromic anemia, with the hemoglobin reduced to 41 to 58 per cent of normal. In treatment the patients were given ferrous iron and a vitamin B preparation of high riboflavin content. There was prompt and permanent relief of their symptoms.

#### ANEMIA ASSOCIATED WITH PREGNANCY

In reporting a hematologic study of 48 cases of pregnancy and reviewing the literature on the anemias of pregnancy, Elliott<sup>68</sup> comments that most of the investigation in this field has been of two varieties: either a mass survey of a large series of cases or a detailed study of individual cases. His investigation was of the latter type. He selected for study 48 patients from an antepartum and obstetric clinic. Most of the patients

were in poor economic circumstances, living in homes of semislum standard. Their diets were mainly carbohydrate. No patient was included if toxemia of pregnancy or other known organic disease was present.

Twenty of the patients were selected as "normals" on the basis of having a hemoglobin content of 80 per cent (Haldane) or over. The color indexes in this group, with 1 exception, fell between 0.8 and 1 and the mean corpuscular volume, also, with the 1 exception, between 73 and 88 cubic microns. The mean cell diameter showed an increased variability, indicating that an abnormal degree of anisocytosis was present in this group. The composite curve of the tests of erythrocyte fragility in hypotonic solutions of sodium chloride showed a slightly increased ease of hemolysis. The reticulocyte counts and plasma bilirubin values were not abnormal.

In the 28 pregnant patients whose values for hemoglobin were below 80 per cent, the value ranged from 32 to 76 per cent and the red blood cell counts from 3,270,000 to 5,000,000 per cubic millimeter. The mean corpuscular volume ranged between 58 and 98 cubic microns. The standard deviation of the red cell diameters and the variability per cent were within normal limits in some persons of the anemic group, although the degree of anisocytosis was a striking feature in many of the films and was associated with considerable variation in staining density. Three patients had a median corpuscular fragility greater than the calculated normal and 21 greater than the observed normal. In the majority of the patients with anemia associated with pregnancy there was a distinct shift toward decreased fragility after parturition as compared with the antepartum reading. This change was observed as early as the fifth day after delivery and for 1 patient was delayed at least nine days. In only 2 patients with anemia was the reticulocyte count raised and then only to a maximum figure of 4 per cent. The plasma bilirubin value fell within normal limits.

The majority of the pregnant women with anemia responded to treatment in the expected manner. Eleven patients were given iron, and only 1, who had an initial color index of 1, failed to respond to both iron and an effective liver extract. Spontaneous improvement after delivery occurred. Four patients in all required blood transfusions.

The increase in median corpuscular fragility differentiates this anemia, irrespective of its other characteristics, from the majority of other anemias. There is as yet no explanation for this change. The abnormal degree of aniso-

<sup>66</sup> Civeira Otermin, F. Plaquetas, leucocitos y mielograma en enfermos de inedia crónica (enfermedad del edema), *Medicina*, Madrid (pt. II) **11** 194, 1943.

<sup>67</sup> Weder, A. Das Plummer-Vinsonsche Syndrom, *Schweiz med Wchnscr* **73** 1354, 1943.

<sup>68</sup> Elliott, G. A. The Anaemias of Pregnancy. A Report on the Haematological Study of Forty-Eight Cases of Pregnancy with a Review of the Literature, *J. Obst. & Gynaec. Brit. Emp* **51** 198, 1944.

cytosis occurring in these patients has been stressed previously as an important sign of abnormal hemopoiesis and is perhaps more significant than the hemoglobin level

The occurrence of some degree of hydremia during pregnancy makes it possible for a hemoglobin content as low as 65 per cent (Haldane) and a red cell count as low as 3,200,000 to be considered physiologic provided certain other conditions are satisfied. The color index must be near unity, the mean cell diameter within normal limits, the values expressing the normal degree of anisocytosis and the mean corpuscular volume within the normal limits for pregnancy.

Several factors may account for the iron deficiency anemia of pregnancy: preexisting anemia, decreased secretion of hydrochloric acid in the stomach during pregnancy, poor social conditions and poor diet, changes in iron metabolism due to pregnancy and the number of previous pregnancies. The number of cases of megalocytic anemia of pregnancy reported in recent years has decreased, and further study is required to elucidate their causes. In the last ten years, not one example of acute hemolytic anemia of pregnancy has been reported. There still remain, however, a group of anemias occurring in pregnancy which it is difficult to fit into any known classification.

Piney<sup>69</sup> presents a short account of the blood disorders of most frequent occurrence during pregnancies, with an unusually good discussion of the accumulated information regarding the macrocytic anemias of pregnancy.

Wiener<sup>70</sup> offers a short comment regarding the macrocytic anemia of pregnancy, which has impressed some observers as resembling a hemolytic anemia. It is well known that the blood of every person contains, in addition to the agglutinogens characterizing the individual, one or more agglutinogens shared by all members of the species. Ordinarily a person does not become immunized or sensitized against antigens contained in his own body, but under certain conditions this principle of "horror autotoxicus" of Ehrlich breaks down. For example, when the sensitized Rh-negative patient is given Rh-positive blood, he breaks down the blood cells. Then the body in disposing of the broken-down cells may occasionally become sensitized to the common species of antigens contained in the stroma. The resulting antibodies have the properties of reacting not only with the

blood of other individuals of the species but also with the patient's own blood cells. The antibodies then act on the patient's own cells, and a hemolytic anemia results. The patient's own broken-down cells may sensitize him still further, and continued hemolysis may result.

By extending this principle of "autoimmunization" to the conditions of pregnancy, a rather attractive explanation of the macrocytic anemias of pregnancy can be suggested. If an Rh-negative mother becomes oversensitized to the fetus' Rh-positive cells, she may also form antibodies to one or more of the common species antigens, and an acute hemolytic anemia could result. This theory stands in agreement with the known clinical characteristics of the disease, and in 3 cases of anemia of this type observed by Wiener the women all proved to be Rh-negative.

#### HEMOLYTIC ANEMIA

*Congenital and Acquired Types*—The general clinical features of the hemolytic anemias, their classification and recent developments regarding their pathogenesis are the subjects of a review by Davis.<sup>71</sup> While in theory a hemolytic anemia is one in which the anemic state results mainly from the process of blood destruction proceeding at an accelerated rate beyond the capacity for blood regeneration, a definition of general value in clinical diagnosis is difficult. Many aspects of the mechanism concerned with the disposal of red blood cells and hemoglobin in health as well as in disease are still obscure. Concerning the destruction of red cells there is little agreement regarding the mechanism beyond the fact that cells damaged by age, trauma or special agents are disposed of by the phagocytic cells of the reticuloendothelial system, predominantly within the spleen. It is still uncertain whether the spleen is the "slaughterhouse" of the red cells, but there is a general consensus that the spleen is certainly their "graveyard." Following the breakup of the red cell, there is phagocytosis of the debris and iron is split off from the hemoglobin. The iron-free compound is converted into bilirubin, which circulates in the plasma, probably in combination with serum protein. The production of this hemobilirubin will obviously be increased under conditions of excessive hemolysis, and there may be increased output of fecal urobilinogen. The determination of the fecal urobilinogen is one of the most important recent advances in the study of the hemolytic anemias.

<sup>69</sup> Piney, A. Blood Disorders in Relation to Pregnancy, Post-Grad M J 20:170, 1944.

<sup>70</sup> Wiener, A. S. Macrocytic Anemia of Pregnancy, J A M A 125:990 (Aug 5) 1944.

<sup>71</sup> Davis, L. J. Haemolytic Anaemias, Edinburgh M J 50:589, 1943.

Under certain pathologic conditions, hemolysis may be predominantly or exclusively intravascular, resulting in the liberation of free hemoglobin in the general circulation. The reticulo-endothelial cells are capable of dealing with only a small amount of free hemoglobin, and when this limit is exceeded the excess breaks down into hematin and globin. Hematin combines with serum albumin to form methemalbumin, a compound which, because of its large molecule, never escapes into the urine. Its demonstration in the plasma by spectroscopic tests is a conclusive indication of intravascular hemolysis. The renal threshold for free hemoglobin is about 150 mg per hundred cubic centimeters. Once hemoglobinuria is established, however, it may continue in the presence of a plasma hemoglobin concentration as low as 30 to 50 mg per hundred cubic centimeters. Thus, hemoglobinuria is another indicator of intravascular hemolysis. While the finding of a sustained high reticulocyte count, nucleated red blood cells, anisocytosis and so forth in the peripheral blood and hyperactive erythropoiesis in the bone marrow are suggestive of excessive hemolysis, unequivocal evidence of such an occurrence may be obtained by demonstrating an increased excretion of fecal urobilinogen, methemalbuminemia or hemoglobinuria.

In familial acholuric jaundice and in sickle cell anemia conspicuous erythrocyte abnormalities are associated with the hemolytic tendency, but the details of the mechanism in each disease are unknown. Nocturnal hemoglobinuria is a form of chronic hemolytic anemia often of considerable severity and displaying a fluctuating course. That intravascular hemolysis occurs has been demonstrated by the finding of increased plasma hemoglobin and methemalbumin. The hemolytic phenomena result from an abnormality of the red blood cells which renders them peculiarly liable to lysis by some agent normally present in the plasma, probably a complement. This susceptibility is aggravated by an increased hydrogen ion concentration, such as occurs during sleep consequent on reduced pulmonary ventilation. Davis had the opportunity to study a patient with this disorder who finally died after an exacerbation of the disease. The effect of  $p_H$  in producing hemolysis could be demonstrated by placing a specimen of the patient's heparinized blood in a tube layered over with paraffin to prevent the loss of oxygen. Hemolysis was evident after a few hours, while control tubes containing normal blood or the patient's blood without paraffin showed no hemolysis.

Hemolytic anemias may result from circulating hemolysins, such as may follow the transfusion

of incompatible blood, sensitization by the Rh antibody, activation of a specific hemolysis in some syphilitic persons by exposure to cold, severe burns, bacterial infections (especially those due to anaerobic organisms) or snake venom. Parasitic infections such as malaria, which is by far the commonest cause of hemolytic anemia, poisons such as lead, phenylhydrazine and phenothiazine and sensitivity to drugs or plants are other etiologic factors which must be considered in diagnosis.

The so-called acquired hemolytic anemias, acute and chronic anemias of unknown cause, comprise a heterogeneous group differing widely in their hematologic and clinical aspects. The prognosis is grave and the mortality rate high. In some cases transfusion may be beneficial or curative and in others of little benefit and productive of hazardous reactions, but this measure should always be tried. The results of splenectomy have varied in different series and no final evaluation is possible.

Davis<sup>72</sup> reports 4 cases of symptomatic or acquired hemolytic anemia with increased urobilinuria, hyperbilirubinemia and reticulocyte counts from 22 to 66 per cent in persons with other primary diseases. Most of them had a personal or family history of jaundice or other manifestation of familial hemolytic icterus. In the first case, a 72 year old man complained of pain in the back and increasing fatigue and weakness and showed pallor, jaundice and hepatomegaly. A severe macrocytic anemia was present, and the reticulocyte count was persistently elevated. Despite treatment he died in a few weeks' time, and necropsy showed that a carcinoma of the pancreas was present, with metastases to the liver, one kidney and the retroperitoneal, mediastinal and cervical lymph nodes. The second case was that of a 19 year old youth who had received roentgen ray therapy three years earlier for a cervical swelling thought to be lymphadenoma. Progressive weakness and pallor developed, and on examination light jaundice, slightly enlarged inguinal nodes and a palpable spleen were found. A normochromic but slightly macrocytic anemia was present, with reticulocytosis. The illness terminated fatally in a few weeks. Permission for an autopsy was not obtained. The third case was that of a 50 year old man in whom a severe hemolytic anemia developed a few weeks after a generalized enlargement of the lymph nodes and splenomegaly had appeared. He had been given a course of

<sup>72</sup> Davis, L. J. Symptomatic Haemolytic Anaemia. A Report of Four Cases, *Edinburgh M. J.* 51:70, 1944.

sulfapyridine without apparent effect. He improved with roentgen therapy and blood transfusions, and during the remaining three years of his life there were no hematologic abnormalities. The diagnosis at autopsy was advanced Hodgkin's disease. The fourth case was that of a 41 year old woman who after being ill for a year with anemia was found to have subleukemic myeloid leukemia. Excessive red blood cell destruction and increased blood regeneration were constantly present during the last week of her illness. Autopsy confirmed the diagnosis of myeloid leukemia. The cause of the hemolysis in these cases remained obscure. There was no evidence of pronounced erythrophagocytosis. It was thought that the tumor growths might have exerted an injurious effect on the circulating erythrocytes, promoting their destruction, or that the activity of the reticuloendothelial cells might have been abnormally stimulated.

A confusing case of symptomatic hemolytic anemia is reported by Feldman and Yarvis.<sup>73</sup> An 18 year old youth complained of bleeding from the gums and passing dark-colored urine. Examination showed that he was jaundiced and that his spleen was greatly enlarged. The hemoglobin content was but 60 per cent of normal, the red blood cells 2,750,000 and the white blood cells 25,000. There were microspherocytosis and reticulocytosis, and the erythrocyte fragility was increased. The differential count included 30 per cent young lymphocytes and 10 per cent abnormal lymphocytes, which were considered to be characteristic of those of infectious mononucleosis. The heterophile agglutination test was repeatedly positive up to a dilution of 1:1,024. Two other hematologists reviewed the findings and agreed in the diagnosis of infectious mononucleosis and hemolytic icterus.

The patient continued to get worse, had many hemorrhagic episodes and required repeated blood transfusions. Finally splenectomy was advised, and a spleen weighing 2,000 Gm was removed. The patient improved temporarily but then failed again. At this time the blood picture was typical of lymphatic leukemia, with the white cell count rising to 230,000.

Neumann<sup>74</sup> reports a somewhat similar case, that of a 51 year old man who became jaundiced and in whom a hemolytic anemia was found. Biopsy of an enlarged lymph node was per-

formed, and a diagnosis of lymphogenous leukemia made.

Concerning the pathogenesis of familial hemolytic icterus, Willenegger<sup>75</sup> discusses the two factors of fundamental importance: (1) the primary, inherited or constitutional anomaly of the red blood cells manifested by their spherocytic forms and diminished osmotic resistance to hypotonic sodium chloride solutions and to lysolecithin and (2) an abnormal activity of the spleen in the destruction of erythrocytes. The constancy of splenomegaly in this disease and the therapeutic benefit of splenectomy illustrate the importance of the splenic factor in the pathogenesis of the disorder, even though splenectomy as a rule does not alter the spherocytosis or increased red blood cell fragility. Some authors have emphasized the function of the spleen in storing erythrocytes in this connection, especially since the spherocytic form and diminished osmotic resistance of the red blood cells occur during their sojourn in this organ. An experiment was planned to evaluate these factors in a patient who was undergoing splenectomy. Seventeen hours before operation 300 cc of fresh type O blood was given to the patient, whose blood was type A. By means of an anti-A hemolysin the donor's and the recipient's erythrocytes in the patient's circulating blood and in the splenic sinuses were later separated for cell counts and morphologic observations.

The majority of the transfused erythrocytes were found to be sequestered in the spleen by the time operation was performed. Those that remained in the circulating blood disappeared somewhat more quickly than would normally be anticipated after transfusion. The transfused erythrocytes recovered from the splenic sinuses seventeen hours after they were injected had already become spheric and even crenated. The donor's cells that remained in the circulating blood showed little or no morphologic change. Blood corpuscles suspended in plasma obtained from the spleen of the person with familial hemolytic icterus showed no morphologic change different from that of those suspended in normal plasma. The author interprets his observations as indicating that the spleen plays an active role in the pathogenesis of familial hemolytic icterus.

Wiedemann<sup>76</sup> discusses the relation of microspherocytosis to decreased osmotic resistance of

73 Feldman, F., and Yarvis, J. J. Manifestations of Hemolytic Phenomena and Infectious Mononucleosis in a Case of Lymphatic Leukemia, *New York State J. Med.* **44** 1693, 1944.

74 Neumann, H. Lymphadenom und hämolytischer Ikterus, *Klin. Wchnschr.* **20** 669, 1941.

75 Willenegger, H. Zur Pathogenese des konstitutionellen hämolytischen Ikterus, *Schweiz. med. Wchnschr.* **74** 491, 1944.

76 Wiedemann, H. R. Familiärer hämolytischer Ikterus und osmotische Hämolyse, *Ztschr. f. Kinderh.* **63** 501, 1942.

the erythrocytes in familial hemolytic icterus. In afflicted families other authors have found as many as 10 per cent of the known carriers of the disease to have normal results of fragility tests. He investigated the family of a 12 year old boy who had had intermittent jaundice from the age of 8 weeks. Both the liver and the spleen were enlarged. A moderately severe anemia was present, with 7 to 15 nucleated red blood cells per hundred white blood cells and a reticulocytosis of 24 to 32 per cent. The mean corpuscular volume was 107 cubic microns. There was no increase, however, in the level at which hemolysis began, although the point of complete hemolysis was definitely above that of the normal control. The mother of the patient and 3 of his sisters had either splenomegaly or jaundice, but there was no alteration in the hypotonic fragility of their cells except for a slightly higher level at which complete hemolysis occurred. The degree of spherocytosis was not pronounced in this family. The author regarded the decreased maximal resistance of the red blood cells as a significant point in diagnosis in atypical cases.

Ducci, Etcheverry, Nijamkin and Zanartu<sup>77</sup> report their observations on 2 brothers who had a form of familial icterus which they considered not to be of hemolytic origin. In 1 boy the features resembled those of familial hemolytic icterus, since there was an elevated blood bilirubin, a slight increase in the red blood cell fragility and an increased elimination of fecal urobilinogen. In the other patient icterus had been present for several years, but the blood values were normal, there was no splenomegaly, and tests of hepatic function, including that of bilirubin excretion, produced normal results. Other relatives were known to be icteric, but they were not available for study.

Horne<sup>78</sup> reviews the general aspects of familial hemolytic icterus of especial interest to surgeons concerned with splenectomy and with the treatment of complications of the biliary tract. When the diagnosis of familial icterus is established, splenectomy is ordinarily advisable at an early age. In competent hands, the operative mortality is low and permanent benefit results. In about 60 per cent of untreated patients with long-standing disease gallstones develop, and in every case a roentgen examination of the gallbladder should be made or the organ

palpated for stone at the time of splenectomy. Perforation of the gallbladder in these cases and the formation of sinus tracts following cholecystotomy occur frequently. Two cases are reported in detail. In 1, a 16 year old girl had recurrent jaundice from early life, and biliary colic developed when she was 15 years old. A splenectomy and cholecystectomy were done in two stages, and the final clinical result was good. The second patient, a 17 year old youth, had had fairly good health in spite of recurrent jaundice and a chronic hemolytic anemia until biliary complications developed. He was operated on for cholecystitis, and the gallbladder, which contained stones, was drained. A cholecystotomy sinus persisted, with periodic passage of stones, and finally jaundice reappeared. The gallbladder was found to have ruptured, causing a bile peritonitis, and a fatal outcome resulted. Splenectomy with early cholecystectomy when gallstones are present is the treatment of choice for this disease.

Hobbs<sup>79</sup> reports 2 cases of march hemoglobinuria occurring in soldiers during training. One 20 year old soldier noted that he passed "bloody" urine after nearly every severe exertion for a period of seventeen days. A slight amount of pain in the region of the left flank accompanied the voiding of the abnormal urine. After the patient was confined to the hospital, several specimens of urine were examined without any abnormality being found and results of a urologic investigation were negative. He was then sent on a trial hike of 10 miles (sixteen kilometers) carrying a pack weighing 34 pounds (15.4 Kg). "Bloody" urine was passed after he had hiked 5 miles (8 kilometers). A specimen of urine obtained on completion of the hike was the color of port wine, the reaction for albumin was 4 plus, the benzidine reaction was 4 plus, and 3 Gm of hemoglobin were present per hundred cubic centimeters of urine. Only an occasional white blood cell was present in the urinary sediment. The hemoglobin content of the plasma rose from 62 mg per hundred cubic centimeters before the hike to 170 mg after the hike. The fragility of the red blood cells in hypotonic solutions of sodium chloride was unaltered. A second soldier, a 32 year old Negro, stated that he had passed "bloody" urine at least twelve times in five months, each time after strenuous exertion. A specimen of urine obtained after a hike was the color of port wine, the reaction for albumin was 2 plus and the benzidine reaction 4 plus. The urobilinogen test showed a

77 Ducci, H., Etcheverry, R., Nijamkin, A., and Zanartu, J. *Istercias familiares hemolitica y no hemolitica*, *Rev. med. de Chile* **71** 837, 1943.

78 Horne, E. O. *Congenital Hemolytic Icterus. Surgical Treatment of Complications with a Report of Two Cases*, *Am. J. Surg.* **65** 56, 1944.

79 Hobbs, R. E. *March Hemoglobinuria. A Report of Two Cases*, *Am. J. Clin. Path.* **14** 485, 1944.

reaction in a dilution of 1:20. The hemoglobin content of the plasma was 80 mg per hundred cubic centimeters. The results of tests of red blood cell fragility with hypotonic sodium chloride and acid were normal.

The author determined the plasma hemoglobin level in 23 men just completing a speed march of 10 miles and found values ranging from 15 to 25 mg per hundred cubic centimeters. In the diagnosis of march hemoglobinuria the significant and constant observations are hemoglobinemia and hemoglobinuria. Concerning its pathogenesis, the author favors the theory of a general intravascular hemolysis.

Makin<sup>80</sup> reports a case of march hemoglobinuria in a 21 year old infantryman which he observed. The soldier noted that he began to pass dark-colored urine after strenuous activity in training and in sports. A urinalysis done after rest showed nothing abnormal. After exercise, however, his urine became dark brownish red in color, the benzidine reaction became positive, and a heavy albuminuria was present, as well as granular casts in the sediment. Spectroscopic examination showed that the urine contained oxyhemoglobin. In four months' time the hemoglobinuria following exercise gradually decreased and finally disappeared. The soldier was subsequently returned to full army duty without ill effects.

Bryce<sup>81</sup> reports a similar case of march hemoglobinuria occurring in an 18 year old soldier. In this patient also aching pain in the groins accompanied the passage of dark urine. This occurred only after unusually strenuous training exercises had been performed. A complete urologic examination was made and no anatomic abnormality found. Finally to establish the diagnosis urinalyses were made after heavy exercise. Under these conditions albumin, free hemoglobin and methemoglobin were present in the urine. The Donath-Landsteiner test failed to reveal paroxysmal hemoglobinuria. Experiments were conducted to determine the amount of work that could be tolerated without producing the hemoglobinuria. The soldier could tolerate working in a stooped position, as in vigorous digging, for at least two hours without symptoms, whereas walking for one to one and a half hours at a brisk pace brought on an attack.

In a discussion of chronic hemolytic anemia with nocturnal hemoglobinuria, Hegglin<sup>82</sup> states

that no form of therapy yet available, including the administration of alkalis and splenectomy, modified the course of the disease materially. He recommended as a palliative measure the use of frequently administered small blood transfusions.

Losada, Etcheverry and Uauy<sup>83</sup> report the case of a 16 year old girl with paroxysmal hemoglobinuria. For five years during the seasons of cold weather she had recurrent episodes of chills, fever and passage of red urine, followed by pallor and icterus. She had had an unusual number of childhood diseases, and when she was 14 years old, enlargement of the cervical lymph nodes developed and examination revealed a tuberculous pleural effusion. The examination of the blood revealed an erythrocyte count of 1,500,000, a hemoglobin value of 50 per cent and a leukocyte count of 2,400. Reticulocytes were increased to 14 per cent, nucleated red blood cells were present, and the average cell volume was 145 cubic microns. The Kahn, Wasseimann and Donath-Landsteiner reactions were strongly positive. While she was under treatment for the tuberculosis, there was progressive improvement in the hematologic status.

Hegglin and Maier<sup>84</sup> describe a "heat resistance" test as a specific test for the recognition of Marchiafava's anemia. This rare disease is characterized chiefly by nocturnal hemoglobinuria and the manifestations of a hemolytic anemia. The hemolysis is produced by the action of a hemolysin whose anboceptor is always present in the erythrocytes but which requires the presence of complement. The degree of hemolysis increases as the temperature of the blood rises and as the  $pH$  of the blood falls.

The test is designed to determine the resistance of the red blood cells to increased temperature. It is performed by putting a test tube containing about 5 cc of blood obtained by means of a syringe sterilized by dry air into the incubator for six to twenty-four hours at a temperature of 37°C. The degree of hemolysis can be observed with the naked eye. Although a quantitative determination of the hemoglobin liberated in the serum is for practical purposes unnecessary, it was done in a series of cases to

82 Hegglin, R. Die chronische hamolytische Anämie mit nachtllicher Hamaglobinurie (Typus Marchiafava), *Helvet med acta* 10:27, 1943.

83 Losada L, A, Etcheverry, R, and Uauy A, N. Hemoglobinuria paroxística esencial (a proposito de un caso clínico asociado a tuberculosis pleural), *Rev med de Chile* 71:1113, 1943.

84 Hegglin, R, and Maier, C. The "Heat Resistance" of Erythrocytes. A Specific Test for the Recognition of Marchiafava's Anemia, *Am J M Sc* 207:624, 1944.

80 Makin, M. A Case of March Haemoglobinuria, *Brit M J* 1:844, 1944.

81 Bryce, L. M. March Haemoglobinuria. Description of the Features of This Condition, and Report of a Case, *M J Australia* 2:49, 1944.

prove the specificity of the test. Two patients with Marchiafava's anemia had serum hemoglobin values of 570 and 675 mg per hundred cubic centimeters after six hours' incubation and 592 and 1,375 mg after twenty-four hours' incubation. The highest value in six other types of hemolytic anemia was 180 mg per hundred cubic centimeters, found after twenty-four hours' incubation. In 50 normal persons, 7 patients with secondary anemia and 12 patients with pernicious anemia there was no increase in hemolysis. The possibility of increased acidity being produced by the heat and causing the hemolysis was not investigated.

Meier<sup>85</sup> reports 2 cases of acute hemolytic anemia of the Lederer-Brill type, which occurred in children. A 3 year old boy, who had previously been well, in a matter of two days' time became greatly fatigued, refused to eat and was constantly drowsy. Examination showed the child confined to bed, febrile, difficult to arouse, pale and jaundiced. Both the liver and the spleen were enlarged. The examination of the blood showed the hemoglobin content to be 20.3 per cent, the red cell count 575,000 and the white cell count 24,400. The reticulocytes were 40 per cent, and many nucleated red blood cells and spherocytes were present. The erythrocyte fragility in hypotonic sodium chloride solutions was slightly increased. Immature myeloid cells were present in the circulating blood. The Wassermann reaction was negative. Intramuscular injections of blood were given on two successive days, as well as *Néoton-Hépar*, iron therapy and symptomatic medication. The child began to improve in three days, was playing actively by the sixth day and later made a complete recovery. There was a transient eosinophilia rising to 16.5 per cent, but the blood picture finally became entirely normal. The parents were given physical examinations and examinations of the blood but no abnormalities were found. The child was still well when last seen sixteen months after the acute illness.

The second child was a 4 year old boy who had had good health until four or five weeks before his admission to the hospital, when fever, obstipation and cramping abdominal pain developed. Shortly afterward he became pale, listless and slightly jaundiced. His condition did not improve. Physical examination showed the boy to be poorly nourished and extremely pale and to have a yellowish complexion. The abdomen was distended, and neither the liver nor the spleen was palpable. Examination of the blood

showed the hemoglobin content to be 16 per cent, the red cell count 1,100,000 and the white cell count 12,500, without unusual immaturity of the myeloid cells. The reticulocytes were increased to 15 per cent, and there were 6 nucleated red blood cells for every 100 white blood cells. There were no spherocytes. It was thought that rupture of the appendix with abscess formation had occurred and that the hemolytic anemia was secondary to this process. Two blood transfusions, sulfathiazole and *Néoton-Hépar* were used in therapy, and the boy recovered in two months.

The author discusses many of the other reported cases of acute hemolytic anemia in children and points out that a dramatic response to blood transfusion is by no means invariable.

Spira<sup>86</sup> reports the case of a 20 month old child in whom an acute hemolytic anemia developed fourteen days after a febrile illness with a cutaneous rash and mild otitis media thought to be scarlet fever. Vomiting, high fever and the passage of dark red urine marked the onset of acute anemia. The child became extremely pale, icteric and finally moribund. The hemoglobin value was 16 per cent, and there was a leukocyte count of 34,000. The erythrocytes showed diminished resistance in hypotonic sodium chloride solutions. A remarkable improvement occurred with the first blood transfusion and subsequently a complete hematologic recovery occurred. An intracutaneous tuberculin reaction was found to be strongly positive, and four weeks after the onset of the anemia there was roentgen evidence of enlargement of the paratracheal lymph nodes. This began to recede after eight weeks of rest in bed, but the primary tuberculous process was kept under observation.

Videla and Bonell<sup>87</sup> report 2 cases of acute hemolytic anemia in adults complicating infectious processes. A 20 year old woman became acutely ill with nausea, diarrhea, abdominal cramps, fever and jaundice. Examination showed that pneumonia with pleuritis appeared to be the primary disease. Anemia, hemolytic in type, with erythroblastosis was present. A single blood transfusion was given, and the patient proceeded to make an uneventful recovery. A similar train of events was observed in a case of a 42 year old man suffering from an infection of the hand with lymphangitis.

86 Spira, M. Zur Frage der akuten, hamolytischen, infektiösen Anämie, Typ Lederer im Kindesalter, *Ztschr f Kinderh* 64 187, 1943.

87 Videla Z, P, and Bonell, J. Eritroblastosis reaccional, 2 casos, *Rev méd de Chile* 71 1204, 1943.

85 Meier, K. Die akute hamolytische Anämie vom Typ Lederer-Brill, *Ann pædiat* 162 140, 1944.

An unusual case of acute hemolytic anemia in a man showing the phenomenon of autoagglutination and autohemolysis at room temperature was studied by Currie<sup>88</sup>. A 37 year old engineer had enjoyed excellent health until he suddenly and without warning felt faint while walking to work. He was forced to sit down, and on attempting to get up he collapsed and lost consciousness for a time. A few hours later progressively deepening jaundice appeared, along with hemoglobinuria. He was hospitalized two days later, when disorientation, confusion and fever had developed. Physical examination revealed extreme weakness, a thready pulse and a tender, palpable spleen. The urine contained hemoglobin and a large amount of hemoglobinous deposit but no bilirubin. Examination of the blood showed that hemoglobin content was 15 per cent, the red blood cell count 900,000, the leukocyte count 25,000 and the icteric index 34. In the blood film there were many normoblasts, some erythroblasts and immature granulocytes. There was obvious microspherocytosis.

The patient's serum was found to agglutinate his own corpuscles at room temperature. His serum agglutinated both group A and group B corpuscles but not normal group O corpuscles. When the blood was typed at body temperature, the patient's cells were found to contain neither A nor B agglutinin. An autohemolysis was shown to be present in the patient's serum which required the presence of complement for its activity. The patient made an uneventful recovery, receiving 1 pint (0.47 liter) of whole citrated blood on the fourth day after his admission to the hospital, at which time he was apparently improving spontaneously. The phenomena of autoagglutination and autohemolysis disappeared during the convalescent period.

Foy, Gluckman and Kondi<sup>89</sup> report a case in which acute erythrocyte hemolysis and severe anemia followed the first administration of benzyl sulfanilamide. Icterus appeared after 12 Gm of the drug had been given, and dark-colored urine was passed after 3 more Gm had been given. Fever and tachycardia appeared, and when a blood transfusion was attempted a severe reaction developed. Oliguria, hypertension and nitrogen retention developed, and the patient died seven days after the initial reaction. At

autopsy the kidneys were found to be deep purple, extremely congested and edematous. There was no mechanical obstruction present in the larger urinary passages, and in histologic sections there was no blockage of the renal tubules with precipitated products of hemoglobin. The authors discuss the blood pigment metabolism in persons with such conditions as blackwater fever, hemolytic jaundice and sulfonamide hemolysis. Oxyhemoglobin, methemalbumin and hemobiliubin are commonly found in all types of intravascular hemolyses. Intracorporeal methemoglobin does not occur in blackwater fever, as far as is known. In the case reported, the intravascular hemolysis and rapid fall in the red cell count were accompanied with the presence of plasma oxyhemoglobin, methemalbumin and hemobiliubin as well as of intracorporeal methemoglobin. Oxyhemoglobin and methemoglobin were found in the urine.

Cole<sup>90</sup> points out that blackwater fever may cause death in two different ways: (1) by fatal anemia due to erythrocyte hemolysis and (2) by renal damage leading to uremia. He presented the case of a young Indian who had a second attack of malaria, for which he took 5 grams (0.32 Gm) of quinine daily. Four days after the onset of the chills and fever, he began to pass dark urine containing a brown deposit, a large amount of albumin and casts. He soon became jaundiced, the hemoglobin content fell to 70 per cent of normal, and the urine became scanty and the color of port wine. Four days later the blood urea level was 104 mg per hundred cubic centimeters, and the urine, although only a few cubic centimeters per day was passed, was clear. A further rise in the blood urea nitrogen to 386 mg per hundred cubic centimeters and generalized edema developed before the urinary output increased and recovery ensued. Four weeks after the onset of the illness, the urine had again become normal, and the urea clearance test showed no evidence of impaired renal function.

Strumia<sup>91</sup> discusses the hemolytic reactions which follow the transfusion of incompatible blood. When transfused blood is incompatible, the recipient's plasma agglutinates and hemolyzes the donor's cells. Clinical signs of a hemolytic reaction start during or shortly after the transfusion and commonly consist of a chill, followed by nausea, vomiting, pain in the lumbar region, a sense of constriction in the chest and fever.

88 Currie, J. P. Acute Haemolytic Anaemia. Report of a Case Presenting Hitherto Unreported Features, *Brit. M. J.* 2: 8, 1944.

89 Foy, H., Gluckman, J., and Kondi, A. Pigment Metabolism and Renal Failure in Acute Sulphonamide Hemolysis Resembling Blackwater Fever, *Tr. Roy. Soc. Trop. Med. & Hyg.* 37: 303, 1944.

90 Cole, A. C. E. A Case of Anuria in Blackwater Fever, *East African M. J.* 20: 381, 1943.

91 Strumia, M. M. Post-Transfusion Hemolytic Reactions, *Pennsylvania M. J.* 47: 668, 1944.

Transient hemoglobinemia followed by oliguria is common. The oliguria may rapidly improve and the patient recover, or azotemia may result and recovery or death ensue after several days. A number of patients have died even though the urinary output has become normal or even greater than normal.

Whenever doubt exists that a hemolytic reaction has occurred, the first urine passed should be examined for albumin, hemoglobin, casts and red blood cells. The blood level of bilirubin should be determined immediately and after five and twelve hours, during which time the peak of bilirubinemia is generally reached.

Strumia does not subscribe to the theory that blockage of the renal tubules accounts for the renal damage associated with transfusion reactions or that alkalinization of the urine is of therapeutic usefulness. The outstanding pathologic lesions in such cases are extremely severe degenerative changes in the epithelium of convoluted tubules, with interstitial edema and vascular embolic phenomena with thrombosis. Since free hemoglobin per se is nontoxic, it appears likely that some factor in the "stroma" of the erythrocytes is toxic, perhaps the A, B or Rh agglutinogens. No therapy has been uniformly successful in treating the renal damage following transfusion of incompatible blood.

The prognosis is poorer for those patients having previous kidney damage or those with other serious illnesses. Most patients receiving 250 cc of blood or less will recover from their first hemolytic transfusion reaction. Those receiving as much as 500 cc or those who have had previous transfusion reactions will usually die.

Precautionary measures include meticulous typing and cross matching, with attention to the Rh factor and to the less common isoagglutinins in special cases. Slow transfusions are advised. Plasma should be used in emergencies rather than blood, even than blood from low titer group O donors with agglutinins not in excess of 1:60.

A serious posttransfusional reaction is reported by Introzzi and Bellotti<sup>92</sup>. A 30 year old woman was prepared for a cholecystectomy for biliary stone. At operation pericholecystitis with a greatly thickened gallbladder wall was found, and the removal of the gallbladder was accomplished with difficulty. A postoperative hemorrhage occurred, and 250 cc of group O blood was given without apparent reaction. The

following day restlessness, drowsiness and subicterus developed. The urinary output gradually fell until it was less than 250 cc per day. Urinalysis gave positive reactions for occult blood, and a few red blood cells were present in the sediment. Lethargy persisted and edema and nitrogen retention were present for several days but the patient eventually recovered.

**Rh Factor**—Wiener, Sonn and Belkin<sup>93</sup> report further study of the heredity of the Rh blood types. Having available three varieties of anti-Rh agglutinins, they were able to demonstrate five kinds of agglutinogens which in combination determine eight types of human blood. Wiener has proposed a theory of six allelic genes to account for the existence of these variants of the Rh agglutinin. The six gene theory postulates the existence of a series of allelic genes, Rh<sub>1</sub>, Rh<sub>2</sub>, Rh', Rh'', Rh and rh, named after the serologic properties which they determine. The gene rh is recessive to the others and in homozygous persons gives rise to the Rh-negative type. The gene Rh' determines an agglutinin Rh', which reacts with anti-Rh<sub>1</sub> but not with anti-Rh<sub>2</sub> or with anti-Rh agglutinins. Similarly the agglutinin determined by the gene Rh'' reacts only with the anti-Rh<sub>2</sub> agglutinin, while agglutinin Rh reacts only with the standard anti-Rh agglutinin, not with anti-Rh<sub>1</sub> or anti-Rh<sub>2</sub>. The agglutinogens determined by the genes Rh<sub>1</sub> and Rh<sub>2</sub>, on the other hand, are each characterized by their ability to react with two of the three primary agglutinins. For example, agglutinin Rh<sub>1</sub> reacts with agglutinins anti-Rh<sub>1</sub> and anti-Rh but not with agglutinin anti-Rh<sub>2</sub>. The capacity of bloods of types Rh<sub>1</sub> and Rh<sub>2</sub> each to react with two distinct agglutinins is inherited as a unit and is assumed to be due to the action of single genes.

With the six gene theory, twenty-one genotypes are theoretically possible. If the phenotype corresponding to each genotype is assumed to represent merely the combined effect of the two genes, then the twenty-one genotypes give rise to eight phenotypes, all but one of which has actually been encountered.

The authors investigated the Rh blood types in 97 families with 275 children and in 135 mother-child combinations. The results obtained were in complete agreement with the theory of six allelomorphous genes. With regard to linkage relations, the authors reported that the genes are transmitted independently of sex, the A-B-O genes and the M-N genes. When active and specific serums are generally available, many

92 Introzzi, A. S., and Bellotti, C. Hemolysis posttransfusional con insuficiencia renal grave, plasmoterapia, Bol y trab, Acad argent de cir 28 6, 1944

93 Wiener, A. S., Sonn, E. B., and Belkin, R. B. Heredity of the Rh Blood Types, J Exper Med 79 235, 1944

clinical applications of these observations will be possible—for example, in transfusion therapy and in the classification of donors. The determination of the Rh type of the father of an erythroblastotic baby will often make possible a more definite statement as to the prognosis of future pregnancies. If the father belongs to type Rh<sub>1</sub>-Rh<sub>2</sub>, all the children must be Rh positive, half Rh<sub>1</sub> and half Rh<sub>2</sub> in the usual case, hence the prospect of the sensitized mother's bearing normal infants with this father is extremely remote. The medicolegal application of the Rh tests and their use in anthropologic studies and in studies of heredity are likewise practical.

Wiener<sup>94</sup> discusses in another report the role of the Rh subtypes in hemolytic transfusion reactions and in erythroblastosis. Analogous problems are presented by the two conditions. In hemolytic disease of the newborn, the Rh antigen is involved in about 90 per cent of the cases. The author encountered an infant with severe erythroblastosis whose mother was reported to be Rh positive. A more complete investigation showed that the father's type was Rh<sub>1</sub>Rh<sub>2</sub> and the child's Rh<sub>1</sub>Rh<sub>2</sub>, while the mother's was actually Rh'. Thus isoimmunization of the Rh-positive mother by Rh-positive fetal blood of a different subtype was proved to be the mechanism responsible for the occurrence of erythroblastosis in the infant. The infant responded well to a blood transfusion of the mother's washed red cells suspended in the father's plasma. In such transfusions it is always safe to use the mother's washed red cells, while it is only generally safe to use Rh-negative blood. Another important corollary of these observations is that Rh-negative blood should be used in transfusions for the mother of an erythroblastic infant even though her blood is Rh positive in tests with the human Rh antiserum on hand. Another case of hemolytic disease of the newborn is described, in which the hemolysis was caused principally by Rh isoantibodies acquired by the infant through ingestion of the maternal milk.

Boorman, Dodd and Mollison<sup>95</sup> studied the incidence of hemolytic disease of the fetus in different families and the value of serologic tests in diagnosis and prognosis. The main features of the relation of the Rh antibody to the

hemolytic disease of the newborn are well established, but much remains to be learned. Although the combination of an Rh-positive infant and an Rh-negative mother occurs in about 95 per cent of all pregnancies, the infant is affected with hemolytic disease in only a small proportion of the cases, for the incidence of hemolytic disease is only 1 in 400, or 0.25 per cent of all pregnancies. The mere demonstration that the mother is Rh negative and the infant Rh positive cannot by itself be regarded as satisfactory diagnostic evidence of hemolytic disease of the fetus. Moreover, the mother has been found to be Rh positive in a small proportion of cases in which the infant was affected with the disease.

The authors studied 100 families in which a fetus suspected of having the hemolytic disease was born, 70 women who had given birth to one or more stillborn fetuses and 60 mothers and their infants thought to have "physiologic jaundice." In the first group 97 of the mothers were Rh negative and 3 Rh positive. Serums of the Rh-negative mothers contained anti-Rh agglutinins in 93 out of 97 instances. Seventy-nine affected infants of Rh-negative mothers were tested and all were Rh positive. Forty-five husbands of Rh-negative mothers tested were all Rh positive. The serums of all 3 Rh-positive mothers contained immune agglutinins incompatible with the fetal erythrocytes. In 1 instance the agglutinin was anti-Rh<sub>2</sub> and in the other 2 the agglutinin was anti-B. When several children were born to sensitized mothers, it was noted that the disease did not necessarily become more severe in successive siblings. In 5 families the birth of an affected infant was followed by the birth of 1 or more normal children. If any of the living children were Rh negative, the prognosis for future siblings appeared to be better.

Of the 70 women who had given birth to one or more stillborn fetuses, 17 were Rh negative and 53 Rh positive. In 11 cases the mother's serum contained immune anti-Rh agglutinins, and in all cases the fetus was stillborn during the last three months of pregnancy. It was concluded that in these cases the fetal death was due to hemolytic disease, while in the remainder this possibility could not be excluded.

Among the group of 60 infants affected with "physiologic jaundice," the mother's serum contained anti-Rh agglutinins in 3 cases out of 60, and in these cases the infant was Rh positive. In only 1 instance did the clinical examination suggest that the infant might have mild hemolytic disease. Compatibility tests between the mother's serum and the infant's erythrocytes with regard to the anti-A and anti-B agglutinins,

<sup>94</sup> Wiener, A. S. Role of the Subtypes of Rh in Hemolytic Transfusion Reactions and in Erythroblastosis, *Am J Clin Path* **14** 52, 1944.

<sup>95</sup> Boorman, K. E., Dodd, B. E., and Mollison, P. L. The Incidence of Haemolytic Disease of the Foetus (Erythroblastosis Foetalis) in Different Families. The Value of Serological Tests in Diagnosis and Prognosis, *J Obst & Gynaec Brit Emp* **51** 1, 1944.

showed that the incidence of incompatibility in this group was not significantly greater than in a random sample of mothers and infants. Cases of mild hemolytic disease of the newborn may sometimes be mistaken for cases of "physiologic jaundice," however, unless serologic tests are carried out.

McCall, Race and Taylor<sup>96</sup> studied an infant with hemolytic disease of the newborn whose mother was Rh positive. The hemolysis was found to be due to a rare type of Rh antibody similar to the anti-Rh factor described by Levine and his collaborators.

Erythroblastosis fetalis in identical twins is reported by Demy<sup>97</sup>. A woman 40 years of age had been pregnant seven times. The first four pregnancies had resulted in living infants. There followed the birth of twins, 1 stillborn and the other dying of hemorrhage in four hours and two years later a stillborn child thought to have had fetal hydrops was delivered. Erythroblastosis was suspected during the last gestation, and investigation showed the father's blood to be Rh positive and the mother's blood Rh negative in high titer. Labor resulted in the spontaneous delivery of identical twin girls. Severe hemolytic anemia with deep jaundice, petechial hemorrhages and a great enlargement of the liver and spleen developed in 1 infant. The other infant had mild anemia, light jaundice and a small percentage of normoblasts in the peripheral blood. Both were given transfusions of Rh-negative blood and recovered, although pigmented skin and an enlarged liver and spleen were still present in the severely afflicted twin fifty-five days after birth. Both infants were Rh positive. Being identical twins they had identical genetic inheritance and were subject to the same titer of antibody from the mother. Demy explains the differing degree of severity of the anemia in the 2 infants as due to a greater functional defect with regard to passage of antibodies in the placenta serving the more severely affected twin.

Keel<sup>98</sup> summarizes the clinical findings in 12 cases of anemia neonatorum with icterus gravis. Four of the infants died and were studied pathologically. Extramedullary hemopoiesis was a constant finding. A group of 21 cases of hemolytic disease of the newborn were investigated by Langley and Stratton<sup>99</sup>.

<sup>96</sup> McCall, A. J., Race, R. R., and Taylor, G. L. Rhesus Antibody in Rh-Positive Mother Causing Hemolytic Disease of Newborn, *Lancet* **1** 214, 1944.

<sup>97</sup> Demy, N. G. Erythroblastosis Fetalis in Identical Twins, *Am J Obst & Gynec* **47** 554, 1944.

<sup>98</sup> Keel, M. Anaemia Neonatorum and Icterus Gravis, *Ann paediat* **160** 179, 1943.

<sup>99</sup> Langley, F. A., and Stratton, F. Hemolytic Disease in the Newborn, *Lancet* **1** 145, 1944.

Previous observations in regard to the role of the Rh factor in this condition were confirmed by finding that in 19 of 21 cases the maternal blood contained an anti-Rh agglutinin. In 12 fatal cases necropsies were done, and in 11 of them extramedullary hemopoiesis was found. The breast milk of 10 of the mothers was examined, and anti-Rh agglutinins were found in the milk of 7.

Van Dorsser, Morrison and Philpott,<sup>100</sup> conducting a study of the significance of the Rh factor in obstetric practice, found that the percentage of abortions, miscarriages and fetal deaths among Rh-negative women was 21 per cent, as compared with 13 per cent among Rh-positive women. The percentage of Rh-negative and of Rh-positive women having no obstetric mishaps, however, were approximately equal. The Rh-negative women during their first two or three pregnancies at least were not particularly more apt to lose their children either before or during birth or in the neonatal period than were Rh-positive women. The incidence of toxemia was about the same in the two groups.

Adelman<sup>101</sup> reports on a pair of dissimilar twins, in 1 of whom severe anemia with jaundice, erythroblastosis, splenomegaly and hepatomegaly developed when the child was 48 hours old. By the use of repeated transfusions the blood values could be maintained, but the infant's clinical condition appeared to become steadily worse. Splenectomy was performed on the thirteenth day, and thereafter an uneventful recovery occurred.

Six infants with hemolytic anemia of the newborn are reported on by Lubinski, Benjamin and Streaan<sup>102</sup>. All the mothers were Rh negative, one of them apparently having been sensitized earlier by transfusions of Rh-positive blood. The authors recommend in treatment the early use of washed Rh-negative red cells. Weiss<sup>103</sup> reviewed the accumulated knowledge concerning the clinical importance of the Rh antigen. He was able to study 15 families in which children with erythroblastic anemia had occurred and others in which the Rh antibody was the cause.

<sup>100</sup> van Dorsser, G. J. E., Morrison, A. W., and Philpott, N. W. Studies on Rh Factor and Its Significance in Obstetric Practice, *Canad M A J* **50** 219, 1944.

<sup>101</sup> Adelman, M. Hemolytic Disease of the Newborn (Erythroblastosis Foetalis) in One of Twins, *Rhode Island M J* **27** 580, 1944.

<sup>102</sup> Lubinski, H., Benjamin, B., and Streaan, G. J. Observations on the Rh-Factor in Its Relation to Hemolytic Anemia of the Newborn Infant, *Am J Obst & Gynec* **48** 464, 1944.

<sup>103</sup> Weiss, C. Rh Antigen Its Clinical Importance, *California & West Med* **60** 59, 1944.

of transfusion reactions or was of interest in medicolegal connections.

Butler, Danforth and Scudder<sup>104</sup> report a serious post-transfusion reaction due to Rh antibody sensitivity. The patient was a 36 year old woman who had given birth to four living children and then had had four spontaneous miscarriages. She became pregnant again, and after five months' gestation fetal movements ceased. A diagnosis of fetal death was made. Two months later, active labor started and a macerated fetus was expelled. After delivery uterine bleeding continued which could not be controlled by ordinary measures and the patient went into mild shock. A transfusion of Rh-positive blood compatible by the usual cross-match method was started and 100 cc given before it was found that the patient was Rh negative. The blood transfusion was stopped immediately and plasma substituted. Forty minutes later the patient had a shaking chill. Bloody urine was passed. The hematocrit value dropped rapidly to nearly half of the original level, and the blood plasma showed hemolysis. The patient became jaundiced and generally edematous. The liver gradually increased in size until its lower edge lay 8 cm below the right costal margin. The cephalin flocculation reaction was then 2 plus.

The patient was given sodium bicarbonate, transfusions of Rh-negative blood and plasma. Extreme oliguria persisted for seven days, nitrogen was retained until the nonprotein nitrogen concentration was 69.2 mg per hundred cubic centimeters, the blood pressure became elevated, and a number of convulsions occurred. Recovery followed.

Investigation showed that anti-Rh agglutinins were present in high titer. The authors advise that blood transfusions never be given to obstetric patients until their Rh type is known.

Howell and Hobbs<sup>105</sup> describe a severe transfusion reaction which occurred in a 45 year old army officer who was given a blood transfusion after an operation for incision and drainage of a deep staphylococcus abscess of the thigh. He had had two blood transfusions about five years previously within a period of two months, and after the second of these he had had a severe chill and fever. The possibility of Rh incompatibility was considered when the third transfusion was given, but no typing serum was available. He was given 400 cc of citrated blood over a period of ninety minutes without

immediate reaction. Forty-five minutes later, however, he had a severe chill, which was followed by a rise in temperature to 102 F. He soon became jaundiced, and during the twenty-four hours following the blood transfusion he voided only 90 cc of urine, containing large amounts of urobilinogen. There was nitrogen retention for several days, but a slow recovery ensued over a period of several weeks. When Rh typing serum was obtained, it was found that the recipient's cells were Rh negative and Rh positive agglutinins were demonstrated in his serum. The donor's cells were Rh positive. The authors emphasize the importance of determining the Rh factor in recipients of repeated blood transfusions, even though the interval may be of several years.

*Elliptocytosis*—The great majority of persons who have the hereditary anomaly of oval or elliptic erythrocytes are healthy persons, long lived, not anemic and not unusually subject to disease. Several years ago Leitner investigated a large family in which elliptocytosis occurred as a benign deformity of the red blood cells. He has more recently<sup>106</sup> encountered another family in which the trait occurred in association with manifestations of hemolytic anemia and he reviews a fairly large number of other reported cases in which this has occurred. In the family he studied 7 of the 8 members showed elliptocytosis, which was inherited as a dominant trait affecting both the males and the females of three generations. The erythrocyte deformity was present in fresh preparations and there was no sickling or alteration in shape with exposure to carbon dioxide. In the 2 persons in whom the erythrocyte deformity was greatest, there was evidence of moderately severe hemolytic anemia with decreased resistance of the erythrocytes to hypotonic sodium chloride solutions, increased bilirubin in the blood and increased urinary urobilinogen. In 1 person the reticulocytes were increased to 38 per cent. There was no splenomegaly observed in any person.

Helz and Menten<sup>107</sup> report a case of elliptocytosis in a 2½ month old Negro child whose father had also had the abnormally shaped red blood cells. In the infant the percentage of oval cells gradually increased to 50 by the age of 4 months, after which no further increase was observed. Tests showed no signs of sickling.

<sup>104</sup> Butler, B. C., Danforth, D. N., and Scudder, J. The Rh Factor in Intragroup Blood Transfusion Reactions, *Surg, Gynec & Obst* **78** 610, 1944.

<sup>105</sup> Howell, R. P., and Hobbs, R. E. A Hemolytic Transfusion Reaction Due to the Rh Factor, *Mil Surgeon* **94** 269, 1944.

<sup>106</sup> Leitner, St. J. Weitere Untersuchungen über die familiäre Elliptozytose der Erythrozyten. Elliptozytose und hamolytische Anämie, *Helvet med acta* **10** 585, 1943.

<sup>107</sup> Helz, M. K., and Menten, M. L. Elliptocytosis. Report of Two Cases, *J Lab & Clin Med* **29** 185, 1944.

Evans<sup>108</sup> studied a Nigerian native in whose blood 94 per cent of the erythrocytes were oval

*Sickle Cell Anemia*—Several authors have contributed studies during the last year showing the wide distribution of the sickling phenomenon among the dark-skinned races. Evans<sup>109</sup> performed tests for sickling on a group of 561 soldiers, natives of the Gambia, the Gold Coast, Nigeria and the Cameroons. Twenty per cent of the entire group had blood which showed sickling in vitro. Of the physically fit soldiers, 15.5 per cent showed sickling in comparison with 25 per cent without sickling among those under treatment for various illnesses. A small group of villagers were examined, and the blood of 18.8 per cent showed sickling. A sex difference was noted in this group since 22 per cent of the males showed sickling but only 13 per cent of the females. No cases of anemia associated with the trait were seen. English<sup>110</sup> reports the presence of the sickle cell trait in a young Bantu man, a native of North Rhodesia.

Mera<sup>111</sup> studied all the school children between the ages of 7 and 17 in Puerto Trejeda, a Colombian town with an 80 per cent Negro population. Of the 489 Negro children examined, 46 (9.4 per cent) showed either the sickle cell trait (5.45 per cent) or sickle cell anemia (3.95 per cent). Typical symptoms of sickle cell anemia in these children included anemia, jaundice, chronic weakness, abdominal colic and ulcers of the leg.

The prevalence of sickle cell anemia in the black Carib Indians, a Negro of relatively pure strain, was studied by McGavack and German<sup>112</sup>. The authors made wet, sealed films of blood from 300 persons living in a small village. Eight per cent of the persons who were studied showed the sickle cell trait. No sickle cell anemia or acute illnesses suggestive of the crises of sickle cell anemia were recognized in these persons.

Castellanos Fonseca<sup>113</sup> reviews much of the literature concerning the sickle cell disease and its general clinical features. Six cases of sickle

cell anemia were reported in detail, in 2 the patients were Negroes and in 4 persons of mestizo origin. Investigation of 1 of the Negro families showed the sickle cell trait to be present in at least 10 males and females in three successive generations.

Triñão and Rôlo<sup>114</sup> review the literature on sickle cell anemia and report on a white Portuguese family in which there were 5 cases in three generations. There was no admixture of Negro blood for at least five generations.

Urteaga Ballón<sup>115</sup> studied the value of splenic puncture as a diagnostic method in cases of latent sickle cell anemia with splenomegaly. In material aspirated from the spleen in such cases large numbers of deformed erythrocytes were present and the procedure was recommended as an aid in diagnosis.

The behavior of erythrocytes from a patient with sickle cell anemia was studied by Murphy and Shapiro<sup>116</sup> under various experimental conditions. A method of making fresh blood preparations using an oiled slide was developed for the rapid demonstration of sickling. The effect on the cells of different serum and saline suspensions was studied, and sickling was found to occur more rapidly and more completely in unaltered whole fresh blood than in either serum or saline suspensions. Experiments confirming the fact that sickling depends on the state of the hemoglobin as regards oxygenation were described. When the hemoglobin was in the reduced form, the sickle shape of the erythrocyte was stable, but with the hemoglobin in oxygen combination the cell reverted to its normal shape. Sickling did not appear to be related to  $p_{H_2}$  or to variations in ionic balance. The potassium content of the erythrocytes, however, appeared to be significantly less than normal, and a preliminary test showed that sickle cells were nearly twice as permeable to the potassium ion as normal cells. The cells of different patients were found to show sickling at different thresholds of oxygen tension. The authors suggest that this phenomenon may be made the basis of a differential test between the sickle cell trait and the sickle cell disease. There was evidence to indicate that as the cells age the sickling threshold becomes lower, which is of possible relation to the genesis of the crises in sickle cell anemia.

108 Evans, W. Elliptical Erythrocytes, *J Path & Bact* **55** 378, 1943.

109 Evans, R. W. The Sickling Phenomenon in the Blood of West African Natives, *Tr Roy Soc Trop Med & Hyg* **37**:281, 1944.

110 English, R. B. Occurrence of Sickle Cell Trait in Blood of Bantu, *South African M J* **17** 389, 1943.

111 Mera, B. Preliminares del estudio de la meniscocitemia en Colombia, *S. A., Bol Ofic san panam* **22** 680, 1943.

112 McGavack, T. H. and German, W. M. Sicklemia in Black Carib Indian, *Am J M Sc* **208** 350, 1944.

113 Castellanos Fonseca, E. Hemodistrofias por hematies falciformes, *Rev med-quir de Oriente* **4** 239, 1943.

114 Triñão, C., and Rolo, J. Anemia de células falciformes, revisão da literatura e apresentação de casos pessoais em brancos portugueses, *Lisboa med* **19** 471, 1942.

115 Urteaga Ballón, O. Importancia de la puncion esplénica en el diagnóstico de la sickle cell anemia, *Rev med exper*, Lima **2** 177, 1943.

116 Murphy, R. C., Jr., and Shapiro, S. Sickle Cell Disease. Observations on Behavior of Erythrocytes in Sickle Cell Disease, *Arch Int Med* **74** 28 (July) 1944.

Winsor and Burch<sup>117</sup> observed that the sedimentation rate in sickle cell anemia was increased by exposing the blood to oxygen and reduced by exposing the blood to carbon dioxide. They describe two methods of making the tests and present data showing that the induced changes in sedimentation rate were constant enough to be of value in diagnosis. The test could be completed in less than thirty minutes in many cases.

The same authors<sup>118</sup> studied a group of 15 patients with sickle cell anemia and 4 patients with the sickle cell trait. Anthropometric measurements, photographs and roentgenograms were compared with the clinical histories and other data. A characteristic habitus, not a primary genetic abnormality but an alteration secondary to the disease, was found in those patients with severe active sickle cell anemia of long duration. Patients with sickle cell anemia only showed no significant deviation from control subjects.

Sickle cell anemia is a disease that is frequently of surgical interest because the crises may simulate acute surgical diseases of the abdomen. Bauer and Fisher<sup>119</sup> report several fatal cases of sickle cell disease, most of them not correctly diagnosed during the life of the patient and urge that routine tests for sickling be made on all Negro patients requiring admission to a hospital. Canby, Carpenter and Ellmore<sup>120</sup> report the case of a 19 year old youth of pure Sicilian stock who became acutely ill with abdominal pain in the left side, fever and leukocytosis. He had been pale most of his life, and some yellowness of the scleras had often been noted. A laparotomy was thought advisable, and an enlarged congested spleen covered with adhesions and fibrin was found and removed. The convalescence was uneventful. His erythrocytes showed complete sickling in twelve hours. There was no sickling in the blood of either parent, four sisters or two brothers after twenty-four hours.

Remhard and his collaborators<sup>121</sup> used oxygen therapy in the treatment of sickle cell anemia. Four patients breathed 70 to 100 per cent oxygen

administered through a Boothby-Lovelace-Bulblian mask for six periods of eight to twenty days each. They observed that oxygen therapy resulted in a decrease in the degree of intravascular sickling of the red blood cells but that there was no consistent detectable change in the rate of hemolysis. Erythrocytogenesis was depressed by the oxygen therapy. On the fourth or fifth day of oxygen therapy the percentage of reticulocytes began to decline, and this decline was followed in two or three days by a fall in the number of erythrocytes, which was occasionally as much as 1,000,000 cells per cubic millimeter. With discontinuation of the oxygen inhalation, a striking reticulocytosis developed and the level of erythrocytes returned to the preoxygen level. No definite conclusions as to the value of oxygen therapy for the crises of sickle cell anemia were drawn.

#### MEDITERRANEAN ANEMIA

Several new studies of Mediterranean anemia have appeared during the past year, showing that anemias of this type are less uncommon and of wider geographic and racial distribution than is generally considered. Among the natives of Cyprus, Fawdry<sup>122</sup> found that erythroblastic, or Cooley's, anemia was a common disease among the children and young adults. He studied 20 patients ranging in age from 6 months to 20 years, all of them, with the exception of 1 Turkish boy, being of Greek ancestry. The general clinical aspects and the conditions observed in the blood and bone marrow in his cases were in agreement with previous studies by other investigators. The use of iron and liver preparations as well as of antimalarial drugs was of no therapeutic value.

Saracoglu<sup>123</sup> reports the typical features of Cooley's anemia in a 9 year old Turkish boy. A brother of the patient had had a greatly swollen abdomen and died of anemia at the age of 5 years. An uncle of the patient was thought to be anemic also. The author stated that his patient was the fourth to be reported on among the Turkish people. Dhayagude<sup>124</sup> reports on

117 Winsor, T., and Burch, G. E. Diagnostic Physicochemical Blood Tests in Sickle Cell Anemia, *Am J M Sc* **207** 152, 1944.

118 Winsor, T., and Burch, G. E. The Habitus of Patients with Sickle Cell Anemia, *Human Biol* **16** 99, 1944.

119 Bauer, J., and Fisher, L. J. Sickle Cell Disease, with Special Regard to Its Nonanemic Variety, *Arch Surg* **47** 553 (Dec) 1943.

120 Canby, C. B., Carpenter, G., and Ellmore, L. F. Drepanocytosis (Sickle Cell Anemia) and an Apparently Acute Surgical Condition of the Abdomen. Report of Their Occurrence in a White Youth with Laparotomy, *Arch Surg* **48** 123 (Feb) 1944.

121 Remhard, E. H., Moore, C. V., Dubach, R., and Wade, L. J. Depressant Effect of High Concentrations of Inspired Oxygen on Erythrocytogenesis. Observations on Patients with Sickle Cell Anemia with a Description of the Observed Toxic Manifestations of Oxygen, *J Clin Investigation* **23** 682, 1944.

122 Fawdry, A. L. Erythroblastic Anaemia of Childhood (Cooley's Anaemia) in Cyprus, *Lancet* **1** 171, 1944.

123 Saracoglu, K. Cooleysche Anämie in der Türkei, *Wien med Wchnschr* **93** 217, 1943.

124 Dhayagude, R. G. Erythroblastic Anemia of Cooley (Familial Erythroblastic Anemia) in an Indian Boy, *Am J Dis Child* **67** 290 (April) 1944.

a 7 year old Brahmin boy, who also showed the blood and skeletal abnormalities typical of severe Mediterranean anemia. Erythrocyte fragility tests and determinations of blood levels of bilirubin on 2 half brothers and a half sister showed them to be normal. The author stated that his patient was the fourth to be observed among Asiatic persons.

A comprehensive study of the hematologic features and the genetic transmission of Mediterranean anemia, or thalassemia, is reported by Valentine and Neel<sup>125</sup>. Hematologic examinations were made on the parents, the siblings and some immediate collaterals of 3 persons who had severe Mediterranean, or Cooley's, anemia and of 1 person with a similar milder condition. The four families included a total of thirty-four persons. Twenty-four of these persons had the mild, benign form of anemia described in recent years by many authors as occurring among families of Mediterranean origin. The mild anemia was qualitatively similar but quantitatively less severe than the full-blown thalassemia and was characterized by increased resistance of the erythrocytes to hemolysis in hypotonic sodium chloride solutions, target and oval red blood cells, microcytosis and hypochromia. All patients with the Mediterranean disease, in the authors' opinion, can be roughly divided into two groups: those with mild, usually asymptomatic anemia and those with severe anemia usually terminating fatally in childhood. It is proposed that these two forms of the disease be designated "thalassemia minor" and "thalassemia major," respectively.

In two families in which there had been children with the severe anemia, or thalassemia major, both parents were available for hematologic examination, and in each family both parents were shown to have significant hematologic abnormalities. In reviewing the literature, the authors found that in every family in which the parents of children with the severe Mediterranean anemia have had complete blood examinations, with 1 possible exception, definite hematologic abnormalities have been demonstrable in both parents. Several possible genetic mechanisms in the heredity of thalassemia have been suggested in the past. The authors believe that it is most likely that thalassemia minor is due to heterozygosity for a factor which when homozygous results in thalassemia major. The problem of the detection of the carriers of thalassemia

and the differential diagnosis of the mild anemia are discussed.

Voorhies and Sloan<sup>126</sup> report the case of a 20 year old youth of Sicilian parentage, who was found, while serving in the United States Army, to have a mild form of Mediterranean anemia. While he was being treated for a poison ivy dermatitis, it was discovered that he was slightly icteric and that his spleen was enlarged with the tip extending to the level of the umbilicus. Except for a tendency to have frequent epistaxes, the inability to run because of pain in the upper left part of the abdomen and shortness of breath on exertion, his general health had been good. There was a moderate degree of anemia present, and the red blood cells varied excessively in size and shape. Ten to 15 per cent of them were target cells. Roentgenograms showed thickening of the calvarium and in other bones osteoporosis with widened trabeculae. Corcoran<sup>127</sup> observed the skeletal abnormalities characteristic of erythroblastic anemia in a roentgenogram of an 8 year old Italian boy who had fractured his femur. Further roentgen study showed the osseous changes to be generalized. The fractured bone healed normally. Novak<sup>128</sup> discovered a number of dental abnormalities as well as prominent trabeculae in roentgenograms of the maxillary and mandibular bones of a child with erythroblastic, or Cooley's, anemia.

#### TOXIC EFFECTS OF INDUSTRIAL POISONS

A general article discussing benzene as a toxic hazard in industry is written by Browning<sup>129</sup>. She reiterates that the extensive use of benzene in industry is largely due to the fact that it is an excellent solvent for many substances such as rubber, nitrocellulose, fat, oils and resins. Unfortunately, despite efforts to prevent toxic effects, they are not infrequently observed, especially in the nervous system and the bone marrow. Hence benzene poisoning is a potential risk to health wherever the substance is used in significant amounts. According to the author, there are two separate fields of application of benzene in industry, each of which carries its own distinct, and to some extent different, risks to health. The first is distillation of coal and

126 Voorhies, N. W., and Sloan, F. R. Mediterranean Anemia, *J. A. M. A.* **125** 352 (June 3) 1944.

127 Corcoran, W. J. Erythroblastic Anemia, with Report of a Case in a Boy 8 Years Old, *Radiology* **43** 373, 1944.

128 Novak, A. J. The Oral Manifestations of Erythroblastic (Cooley's) Anemia. Case Report, *Am. J. Orthodontics* **30** 539, 1944.

129 Browning, E. Benzene as a Toxic Hazard to Industry, *Brit. J. Phys. Med.* **7** 122, 1944.

125 Valentine, W. N., and Neel, J. V. Hematologic and Genetic Study of the Transmission of Thalassemia (Cooley's Anemia, Mediterranean Anemia), *Arch. Int. Med.* **74** 185 (Sept) 1944.

coal tar, in which the risk is chiefly that of acute poisoning or "gas." This most frequently arises from accidental leakages or breakages or from the failure of the worker to take full precautions when entering vats or tanks for the purpose of cleaning them. The second is the use of benzene as a solvent or a diluent, as in the rubber and lacquer industries, airplane "doping" and manufacture of artificial leather, in which the risk is mainly that of chronic poisoning, with its attendant symptoms and hematologic changes. Benzene poisoning, therefore, results either from absorption from the skin or from inhalation, and it is imperative that contact by either of these routes should be reduced to a safe level. A diagnosis of chronic benzene poisoning cannot be made on the evidence of symptoms alone, for hematologic changes do not by any means always run parallel with the severity of subjective symptoms nor are either the hematologic changes or the damage to the bone marrow invariably characteristic. Although aplastic anemia is the most frequent outcome of severe benzene poisoning, there have been cases in which the final condition is that of leukemia, in which the bone marrow has been found after death in a state of hyperplasia or of combined hyperplasia and aplasia. According to the author, however, it is clear that the earliest signs of benzene poisoning is a reduction of those elements of the blood stream which are believed to provide the body with its powers of resistance to infection, namely, the polymorphonuclear leukocytes. Even though the white blood cell count is 5,000 to 6,000 per cubic millimeter, the differential count of the stained smear in affected patients will show change in the proportion of polymorphonuclear leukocytes, so that the total number of these cells is below 3,000 per cubic millimeter. If the workers are removed from the exposure to benzene at this stage, there is every reason to believe that the depressed bone marrow will recover and that no permanent ill effects will remain. When the damage has progressed to the stage of true aplastic anemia, blood transfusions and injections of pentnucleotide are sometimes successful, but if the degree of aplasia is extreme, no treatment seems to be efficacious. The important observation is emphasized that all persons who come into contact with benzene are not equally susceptible to its toxic effects. Among a large number of workers who are equally exposed for the same length of time and to the same concentration, only a few may have any symptoms of ill health or show any characteristic hematologic change. On the other hand, extremely severe poisoning

may arise in any susceptible person with only moderately severe exposure.

A report of a case of fatal poisoning with benzene is given by Ackerly and Hawlick.<sup>130</sup> The patient was a man 35 years old, who was exposed to benzene as a result of rinsing glassware with it six to eight times a day. This required ten to fifteen minutes for each operation. When the patient was admitted to the hospital, his hemoglobin content was 34 per cent, red blood cell count 1,550,000 per cubic millimeter, with 37 per cent reticulocytes, and white blood cell count 3,450 per cubic millimeter, with 10 per cent stab forms, 40 per cent segmented forms and 50 per cent lymphocytes. The platelet count was 171,000 per cubic millimeter, bleeding time three minutes ten seconds and coagulation time three minutes forty-five seconds. Despite all treatment, the patient died. Observations at necropsy showed, among other things, reduction in the total number and irregularity in the distribution of the myeloid elements. The erythroblastic elements were represented by small clumps of dark-staining cells, chiefly normoblasts. Megakaryocytes were numerous and irregularly spaced, and there was pronounced variation in their size, shape and nuclear configuration. All the myeloid elements were present, but mature granulocytes were less numerous than normal.

A report on a patient in whom thrombocytopenic purpura due to benzene poisoning developed is presented by Vaughan,<sup>131</sup> and the literature bearing on this subject is discussed. He makes the point that depressed production of platelets is a commonly associated phenomenon in benzene poisoning but that cases of thrombocytopenic purpura unassociated with striking changes in other marrow elements are rarely found. The patient observed by Vaughan was a woman 33 years of age, whose chief complaint was menorrhagia of nine months' duration and purpura of sixteen months' duration. She was first seen by a surgeon, who performed a dilation and curettage and finally implanted a radium bomb for eighteen hours. A short time later the patient was admitted to the medical service of the hospital and showed the classic hematologic features of thrombocytopenic purpura. The platelet count was 20,000 per cubic millimeter, bleeding time eighteen minutes, clotting time eleven minutes and clot retraction 47 per cent of

130 Ackerly, R. H., and Hawlick, G. F. Benzene (Benzol) Poisoning. Report of a Fatal Case with Autopsy Findings, *Rocky Mountain M. J.* **41** 402, 1944.

131 Vaughan, W. T., Jr. Thrombocytopenic Purpura Due to Benzol Poisoning, *J. Indust. Hyg. & Toxicol.* **26** 274, 1944.

normal The tourniquet test resulted in 159 purpuric spots to the square inch with 10 spots in the control The prothrombin time was fifty-five seconds (the control was forty-five seconds) and the ascorbic acid level was normal Aspiration of sternal marrow revealed an essentially normal marrow picture with no increase in megakaryocytes The patient reported that for sixteen years between the ages of 14 and 31, she had worked in various shoe factories as a "cementer" At this time she handled all kinds of cement, which dried on her hands in the course of her work Just prior to the first episode of purpura, however, the patient had terminated a four month period of cementing in a factory reported not to be using benzene as a solvent Vaughan estimates that the interval between exposure and the development of clinical symptoms in his patient was approximately six to twelve months Whereas undoubtedly benzene must be considered as an important etiologic factor in the production of purpura in this patient, it is not proved beyond the question of a doubt that it was the responsible cause The case emphasizes however, the care with which the history must be taken in all cases of diseases of the blood which might be attributable to the effects of various industrial poisons or toxins A further follow-up study of this patient would be of extreme interest, to learn whether some other disease condition, such as a subleukemic leukemia or true idiopathic thrombocytopenic purpura, might develop

Cone<sup>132</sup> reviews the literature concerning the effect of trinitrotoluene (TNT) on the blood and studied a group of workers exposed to this chemical in a munitions industry Weekly blood counts were performed on 17 workers in intimate contact with trinitrotoluene for eight weeks and then monthly for an additional four months During the period of study the trinitrotoluene concentration of the air was determined and found to be consistently below the proposed threshold level of 25 mg per cubic meter of air In all there was relatively little change in the erythrocyte count during the investigation, and there were no changes in the size and shape of the red blood cells The hemoglobin level was not affected Most of the persons studied showed a transient initial rise of leukocytes the count usually varying from 11 000 to 12 000 per cubic millimeter and there was a moderate eosinophilia but in some instances the proportion of eosinophils was as high as 15 per cent The

hematologic changes were not accompanied with symptoms No other alterations were noted in the formed elements of the blood

Three fatal cases of trinitrotoluene poisoning are reported by McNally<sup>133</sup> He reviews the literature and points out that trinitrotoluene may gain entrance into the blood stream by absorption through the skin, lungs or gastrointestinal tract Unless masks are worn, fine dust and fumes will reach the mucous membranes of the nose and mouth and be swallowed with the saliva and mucous secretions There seems to be general agreement that the skin is the most important portal of entry He states that the outstanding features of trinitrotoluene poisoning are the changes found in the blood, jaundice, degenerative hepatitis (the liver being reduced to one half of its normal weight) and the renal damage The hematologic changes are described as varying considerably, depending on the intensity of the exposure and the length of time the person has been employed on the particular job Sometimes there is extensive anemia, with a hemoglobin content reported as low as 28 per cent and a red blood cell count of 1,225,000 per cubic millimeter with a variation of the white blood cells from 2,800 to 14 650 According to McNally, two theories have been advanced as to the origin of the anemia Some investigators believe the hepatic injury to be the primary source while others assume that the destruction of the red blood cells is the cause of the icterus and that it is therefore of hemolytic origin

The uses of tetrachloroethane in industries associated with war activities are described by Coyer<sup>134</sup> and 7 cases of poisoning with this chemical are described It is a colorless, mobile liquid with an odor resembling that of chloroform and carbon tetrachloride is nonflammable and has been used as a solvent for various substances, such as cellulose acetate and nitrate resins waxes, pitch and various other materials It is the most toxic of the chlorinated hydrocarbons and produces not only a narcotic effect but profound metabolic injuries, especially atrophy of the liver Reference to the original article should be made for details of the toxic effect The changes in the blood are not striking There usually is a moderate reduction in the red blood cell count, to the vicinity of about 3,500,000 red blood cells per cubic millimeter, a moderate increase of leukocytes, the count varying from

133 McNally, W D Three Deaths from TNT (Trinitrotoluene) Poisoning, *Indust Med* 13 491, 1944

134 Coyer, H A Seven Cases of Tetrachloroethane Poisoning and Review of Several Cases Treated, *Hahne-man Monthly* 79 230, 1944

132 Cone, T E, Jr Review of Effect of Trinitrotoluene (TNT) on Formed Elements of Blood, *J Indust Hyg & Toxicol* 26 260 1944

11,000 to 13,000 per cubic millimeter and no other changes of importance in the blood

It has been found by Van Loon and Clark<sup>135</sup> that the administration of acetanilid up to 36 mg per kilogram per day over long intervals caused little or no abnormal hematologic changes in dogs. Larger doses of the drug, however, produced a hemolytic anemia but with no evidence of depression of the bone marrow. Recovery was rapid and apparently complete on cessation of administration of the drug. The same effect was produced by the administration of acetophenetidin, but quantitatively the drug is less active than acetanilid. A temporary methemoglobinemia is produced by both drugs when certain threshold doses are exceeded. In the range of the dose employed, however, no accumulation of methemoglobin was observed in repeated daily administrations.

#### APLASTIC ANEMIA

A general discussion of aplastic anemia is given by Pearce,<sup>136</sup> in which he makes the following main points. First, in all cases of anemia in which the bone marrow shows signs of regeneration there should be a thorough search made for the offending agent and, if possible, it should be eradicated. Second, not all the diagnostic criteria are present in every case of early aplastic anemia, since depression of granulocyte or thrombocyte formation may not develop until some time after depression of erythrocyte formation. He also properly emphasizes that even signs of regeneration of erythrocytes may be apparent at times as evidenced by a patchy condition of the marrow. Third, he insists that treatment should be persistent. It is his opinion that as long as there is life there is hope that a plastic or even aplastic marrow may ultimately become regenerative. Fourth, he emphasizes that repeated blood transfusions are still the main source of treatment but that marrow transfusions should be given further trial. We have observed spontaneous remissions in the course of idiopathic aplastic anemia, and we therefore agree that treatment should be persistent. We have also seen, as a result of one hundred and thirty-eight blood transfusions administered to 1 patient over a course of eight years, the development of hemochromatosis, presumably resulting from the injection of the iron contained in the hemoglobin of the transfusions. This is a matter which should be kept in mind.

<sup>135</sup> Van Loon, E. J., and Clark, B. B. Observations on Hematologic Actions of Acetanilid and Acetophenetidin in Dog, *J. Lab. & Clin. Med.* **29** 942, 1944.

<sup>136</sup> Pearce, R. S. Hypoplastic or Aplastic Anaemia, *Memphis M. J.* **19** 51, 1944.

A patient with aplastic anemia is discussed by Halliday<sup>137</sup> in whom the characteristic blood picture was present. This patient had been treated for sore throat with intravenous injections of 2.1 Gm of a French preparation of neoarsphenamine. Subsequently, owing to a recurrence of the inflammation, the patient received several courses of sulfapyridine and sulfathiazole. The red blood cell count was found, when determined for the first time after both forms of medication had been given, to be 3,100,000 per cubic millimeter, the hemoglobin content was 8.2 Gm per hundred cubic centimeters, and the leukocytes numbered 2,700 per cubic millimeter, 5 per cent being neutrophils. Blood platelets were "scanty." The bleeding time was twenty minutes. Hemolytic anemia resulting from the untoward effects of the sulfonamide drugs is also discussed by Halliday. In general, he believes that the toxic reactions due to the sulfonamide compounds result from (a) ill considered administration, (b) careless management of the patient, (c) prolonged course of treatment (over ten days) and overdosage and (d) allergic idiosyncrasy and sensitization. In treating agranulocytosis, in addition to immediate withdrawal of the drug, he recommends repeated blood transfusions and injections of sodium pentnucleotide. In his opinion, the value of liver extract and preparations of bone marrow appears doubtful. In treating patients with thrombocytopenic purpura due to sulfonamide compounds, the suspension of the use of the drug and repeated transfusions are recommended. In treatment of hemolytic anemia, he favors repeated blood transfusions and use of alkalis and later oral administration of iron.

Fatal bone marrow intoxication following exposure to trinitrotoluene is described by Hart and his associates<sup>138</sup> and by Eddy.<sup>139</sup> The former report 4 cases and the latter reports 3, but apparently 1 case is included in both series. All the patients were employed in munition plants. The duration of exposure to trinitrotoluene varied from thirty days to eleven months. One of the patients, a 26 year old man, reported on by Eddy, was employed in the shipping room of a bomb line, where there was no demonstrable trinitrotoluene in the air. All the others in both series were exposed to concentrations of the chemical

<sup>137</sup> Halliday, J. A. Aplastic Anemia, *M. J. Australia* **1** 352, 1944.

<sup>138</sup> Hart, W. L., Ley, E. B., Scroggie, V. D., Johnson, E. A., and Eddy, J. H. Jr. Report of Four Cases of Aplastic Anemia Occurring Among Munitions Workers, *Indust. Med.* **13** 896, 1944.

<sup>139</sup> Eddy, J. H., Jr. Aplastic Anemia Following Trinitrotoluene Exposures. A Report of Three Cases, *J. A. M. A.* **125** 1169 (Aug. 26) 1944.

ranging from 1 to 107 mg per cubic meter of air. The clinical course was typical of myeloid aplasia, with anemia, hemorrhagic manifestations and intercurrent infection. The duration of symptoms varied in different patients from about two weeks to seven months. Therapy was of no avail, except for temporary benefit from blood transfusions, and death usually occurred as the result of hemorrhage or infection, although in 1 case a contributing factor appeared to be reaction to blood transfusions with hemolysis and hepatic damage. In all instances in which examinations of marrow were performed, a pronounced degree of hypoplasia was found affecting both the erythropoietic and the leukopoietic elements. Although Hart and his associates state that "the most dependable laboratory finding indicative of toxic reaction is the reduction in the hemoglobin and red blood count," it is our opinion that the leukocyte count and neutrophil percentage constitute an earlier and more sensitive index of marrow intoxication.

Aplastic anemia complicating therapy with oxophenarsine hydrochloride for syphilis is reported by Freeman<sup>140</sup>. His case was that of a 37 year old soldier who had received treatment with neoarsphenamine irregularly over a period of two years with several febrile reactions but no other toxic manifestations. After an interval of approximately three months following the last injection of neoarsphenamine, treatment with oxophenarsine hydrochloride was begun. After the tenth injection of the latter drug purpura appeared, but, in spite of this, two more injections were given. The patient died nineteen days after he had first noted the purpura. Findings at necropsy included severe ulceronecrotic lesions throughout the mouth and upper respiratory tract, multiple hemorrhages in skin, mucous membranes and serous membranes and bilateral lobular pneumonia. There was aplasia of all cellular elements of the bone marrow. Two other previously reported cases of aplastic anemia following use of oxophenarsine hydrochloride are reviewed.

The diagnosis of osteosclerotic anemia or the anemia associated with Albers-Schonberg disease, is discussed by Binder and Riedl<sup>141</sup> in reporting 2 cases. The diagnosis was suspected first in both instances when great difficulty was encountered in doing sternal punctures. The

first patient was a 29 year old mason, who complained of weakness, shortness of breath and bleeding from his nose and gums for two months. The liver and spleen were found to be slightly enlarged. The hemoglobin content was 55 per cent, red blood cells 2,900,000, white blood cells 7,000, hematocrit reading 24 and average cell volume 82 cubic microns. The differential count included a few myelocytes and about 1 nucleated red blood cell for every 100 white blood cells. The reticulocytes were 55 per cent. There was severe thrombopenia. A sternal puncture was impossible, since the needle broke in the attempt to penetrate the hard bone. Roentgenograms were then obtained, which showed generalized increase in skeletal density and bony sclerosis. The patient finally died of a generalized tendency to bleeding. Necropsy revealed generalized overgrowth of bony and fibrous tissue, with obliteration of the marrow cavity. There was no definite evidence of extramedullary blood formation. The second patient was a 42 year old man who had been weak and anemic for six months following a febrile illness. Blood transfusions and injections of liver extract had been of little benefit. The erythrocyte count was 1,800,000, hemoglobin content 37 per cent, hematocrit reading 17 and average cell volume 94 cubic microns. Ten per cent of the white blood cells were myelocytes. The reticulocyte percentage was 6. Sternal puncture was attempted but could not be done because of the dense bone. Roentgenograms of the bones showed greatly increased density, thickening and sclerosis. The patient improved after a series of blood transfusions.

#### TOXIC EFFECT OF THE SULFONAMIDE DRUGS INCLUDING AGRANULOCYTOSIS

An informative and reliable article dealing with the toxicity of sulfonamide drugs is presented by Lyons and Van Harn<sup>142</sup>. The authors cite statistics to show that toxic manifestations, such as fever, rash, hemolytic anemia, leukopenia, agranulocytosis, hematuria, oliguria and hepatitis, are present in about 12 per cent of the patients receiving sulfanilamide, in 15.9 per cent receiving sulfapyridine, in 18.6 per cent receiving sulfathiazole and in 6.5 per cent receiving sulfadiazine. They state that experience with sulfamerazine and sulfamethazine is as yet insufficient to permit cleancut decisions concerning the incidence of toxicity of these drugs. There is evidence to indicate, however, that sulfamerazine has about the same toxicity as sulfadiazine. Their state-

<sup>140</sup> Freeman, H. E. Aplastic Anemia with Acute Agranulocytosis, Thrombopenic Purpura and Complicating Mapharsen Therapy. *Arch Dermat & Syph* 50:320 (Nov.) 1944.

<sup>141</sup> Binder, L., and Riedl, O. Beiträge zur Diagnostik der osteosklerotischen Anämie, *München med Wchnschr* 89:519, 1942.

<sup>142</sup> Lyons, R. H., and Van Harn, R. S. Problems of Toxicity in Sulfonamide Therapy, *J Oral Surg* 2:118, 1944.

ment in regard to the hematologic disorders which result from sulfonamide therapy may be summarized briefly as follows. They emphasize that such disorders as agranulocytosis, acute hemolytic anemia and thrombopenic purpura are uncommon but exceedingly serious complications of this form of treatment. They are encountered less often with sulfathiazole therapy than with sulfapyridine or sulfanilamide therapy, a point which we believe requires confirmation.

It is not clear whether these untoward results are due to hypersensitivity or whether in some cases they may be a result of direct toxic effect of the sulfonamide drugs. According to Lyons and Van Harn, hemolytic anemia is most likely to occur from the third to the fifth day of treatment, and it appears to be an expression of an individual idiosyncrasy to the drug. A more slowly developing anemia associated with hemolysis of the erythrocytes is not infrequently seen with sulfanilamide therapy and especially with sulfapyridine therapy, but it rarely occurs with sulfathiazole or sulfadiazine therapy. It is usually not an important complication of treatment, since it can be easily controlled by transfusions.

It has been noted by the authors that thrombopenic purpura has followed the use of sulfathiazole and sulfadiazine as well as the use of the earlier sulfonamide compounds. They state that too few cases have been studied to be certain whether this is the result of a direct toxic effect on the bone marrow or of an individual idiosyncrasy to the drug. The authors point out that, in contrast to acute hemolytic anemia and thrombopenia, it is uncommon for leukopenia or agranulocytosis to occur early in the course of sulfonamide therapy. These complications most frequently develop between the fifteenth and twenty-fifth days of treatment. In some cases readministration of the drug causes a recurrence of the agranulocytosis, but not in all instances. They emphasize that there is a second type of leukopenia in agranulocytosis, perhaps related to the lowering of the intestinal synthesis of essential growth factors through the administration of succinylsulfathiazole or sulfaguanidine. In animals this type of agranulocytosis is benefited by the administration of a liver extract.

The toxic effects of sulfonamide drugs are discussed by van Dyke<sup>143</sup> in a symposium dealing with these drugs. He emphasizes among other untoward effects the frequency of leukopenia and agranulocytosis. He states that "probably there have been hundreds of fatalities." He believes that granulocytopenia or agranulocytosis

is usually observed in patients who receive large total doses of sulfonamide drugs over periods of eighteen to twenty-five days. It is his opinion that the complication rarely appears earlier than twelve days after the beginning of treatment, which has also been borne out in our experience. He cites the case of 1 patient reported on in the literature, who received 54 Gm of sulfanilamide during nineteen days and of another who received 44 Gm of the drug in twenty-five days before this complication appeared. He recognizes that any one of the sulfonamide drugs may provoke granulocytopenia and agranulocytosis but that the appearance of the syndrome has been reported more frequently after the administration of sulfanilamide, perhaps because the total number of patients treated with this drug is greater than the number of patients treated with any other sulfonamide compound.

Van Dyke also discusses the occurrence of hemolytic anemia due to treatment with sulfonamide drugs. He believes that a drug like sulfanilamide probably causes this change more frequently in children than in adults. Hemolytic anemia may result from the use of sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine or diaminodiphenylsulfone. Rarely, in his opinion, does aplastic anemia develop from the use of these therapeutic agents. He believes that perhaps as satisfactory a hypothesis as any relating to the cause of hemolytic anemia is the one that it results from increased fragility of the erythrocytes, attributable to the oxidation products of the sulfonamide drugs. It is also mentioned by Van Dyke that thrombopenia with purpura is a rare complication of sulfonamide therapy, of which about half the reported cases have terminated fatally.

The toxic reactions in 1,936 patients treated with sulfathiazole, sulfadiazine, sulfapyrazine, sulfaguanidine and succinylsulfathiazole are reported by Vilter and Blankenhorn<sup>144</sup>. Toxic reactions were found to occur in 116 patients, an incidence of 6 per cent. These untoward manifestations were usually of such severity as to compel the arrest of treatment. Occasionally therapy could be resumed by changing to another drug, and this was most frequently done by substituting sulfadiazine for sulfathiazole. Death was ascribed solely to the toxic effects of these drugs in 4 instances (0.2 per cent), and in 5 other patients it was certainly hastened by drug intoxication. All fatal toxic reactions were mainly renal and resulted in uremia. Altera-

<sup>143</sup> Van Dyke, H. B. The Toxic Effects of the Sulfonamides, *Ann New York Acad Sc* **44** 477, 1943

<sup>144</sup> Vilter, C. F., and Blankenhorn, M. A. The Toxic Reactions of the Newer Sulfonamides, *J A M A* **126** 691 (Nov 11) 1944

tions in the blood and bone marrow were noted 11 times with the use of sulfathiazole, once with sulfapyrazine and not at all with sulfadiazine. Of the patients who received sulfathiazole, hemolytic anemia developed in 4, leukopenia in 5 and agranulocytosis in 2. All patients recovered. In 1 patient who received sulfapyrazine leukopenia developed. In a discussion of this article, Dr S L Bernstein, of Cleveland, warns against prescribing sulfonamide drugs to ambulatory patients. He remarked that he had given a man aged 60 a small dose of sulfanilamide for septic sore throat. The patient received a total of 20 grains (1.3 Gm) with alkali for three days, and agranulocytosis developed, from which he recovered. This seems to be a small amount of sulfanilamide to be responsible for the development of agranulocytosis, especially if the patient had not previously received the drug.

In reviewing the type and frequency of reactions in 186 cases of sulfonamide intoxication, it was noted by Frist<sup>145</sup> that leukopenia occurred in 2 of 33 patients given sulfanilamide, 2 of 16 patients given sulfapyridine and 2 of 71 patients given sulfathiazole. A "secondary anemia" occurred in 5 patients of the 33 receiving sulfanilamide, 1 of the 16 receiving sulfapyridine, 2 of the 60 receiving sulfadiazine and in 4 of the 71 receiving sulfathiazole. In a total of 186 cases, therefore, there were 12 cases of "secondary anemia" and 6 cases of leukopenia.

Kracke,<sup>146</sup> in discussing hematologic problems before the Section on General Practice of the Southern Medical Association in November 1943, stated that an "occasional patient" may show a depression of the bone marrow from the action of sulfonamide drugs to the extent that the white blood cell count is extremely diminished and that the condition of agranulocytosis may subsequently develop. He also stated that he had seen 6 patients in whom there had been a pronounced thrombopenia following the use of these drugs. He regarded this as a serious clinical problem, since 4 of his patients died from resulting uncontrollable hemorrhages.

A study of the toxic reactions which occurred in 1,357 hospital patients treated with sulfadiazine orally or sodium sulfadiazine intravenously is reported by Plummer and Wheeler.<sup>147</sup>

Of this entire group, a definite drop in the number of white blood cells below 3,000 per cubic millimeter or in the percentage of granulocytes below 35 was observed in only 6 patients, but in none of these did the total white blood cell count fall below 2,000 per cubic millimeter or the percentage of granulocytes below 10. There were no changes in the red blood cells observed. In 1 of the surgical patients, however, a fatal thrombopenia occurred after six days of treatment with sulfadiazine in a dose of 6 Gm daily. This was the only fatal toxic reaction in the group.

Three fatal cases of streptococcal infection treated with sulfadiazine are reported by Geever,<sup>148</sup> with complete autopsy observations. There were no changes in the peripheral blood or bone marrow observed in the patients. A good point is emphasized by Geever, however, with which we are in complete accord, namely, that if a decision to continue the use of the drug in treatment of any patient in whom a cutaneous eruption develops during sulfadiazine treatment is made, then toxic effects should be expected and weighed against any possible beneficial influence on the original infection. In other words, the presence of a cutaneous eruption is a definite warning that subsequent important complications, of which agranulocytosis is the most serious, may be observed if the medication is continued.

Three fatalities following the use of sulfonamide drugs are reported by Gessler,<sup>149</sup> and a review is given of 30 additional cases, with necropsies, which were reported in the literature. In 5 of the 30 cases, agranulocytosis was a complicating factor, twice being due to the use of sulfathiazole, twice to sulfapyridine and once to sulfanilamide. In no case reported in this group did the complication follow the use of sulfadiazine. In most instances the dose was 6 Gm per twenty-four hours, the average daily dose never exceeded 10 Gm. From his study the author concludes that uremia and agranulocytosis are the most frequent lethal complications. Sulfathiazole, according to him, has more chance of causing urinary complications than have other drugs. He states that the microscopic picture of the bone marrow in cases of agranulocytosis due to sulfonamide intoxication is usually that of arrest of cell maturation. He quotes, however, from the article by Lederer and Rosen-

145 Frist, T F. Reactions to Sulfonamide Compounds. Review of One Hundred and Eighty-Six Cases, *War Med* 5 150 (March) 1944.

146 Kracke, R R. Hematologic Problems in General Practice of Medicine, *South M J* 37 90, 1944.

147 Plummer, N, and Wheeler, C. Toxicity of Sulfadiazine. Observations on 1,357 Cases, *Am J M Sc* 207 175, 1944.

148 Geever, E F. Pathologic Changes in Sulfadiazine Intoxication, *Am J M Sc* 207 331, 1944.

149 Gessler, C N. Deaths from Sulfonamides, A Clinical and Pathological Study, with a Report of Three Cases, *South M J* 37 365, 1944.

blatt,<sup>150</sup> in which reference is made to the occurrence of areas of focal necrosis in the bone marrow, which were similar to the focal necrotic areas seen in other organs. The patients in these cases, however, did not have agranulocytosis. It is the opinion of Gessler that the lesions of focal necrosis, agranulocytosis and periaortitis nodosa may all be due to a combination of biochemical, pharmacologic and allergic reactions.

A general discussion is given of the favorable effects of sulfonamide compounds, and reference is made to the little understood mechanism of the toxicity of these drugs. It is stated that the toxic phenomena are related to the concentration of the sulfonamide compounds in the blood and the duration of treatment with them but that these phenomena may occur in the absence of excessive blood concentration or prolonged therapy. Hence, these are not the sole factors. To say that the toxic reactions are due to an idiosyncrasy is "begging the question," since so little is known relative to aberrant drug responses. In the opinion of the authors, sensitization appears to assume a role in some cases. They also emphasize the recent work indicating that the less absorbable sulfonamide compounds may cause vitamin deficiencies by decreasing the number of bacteria in the intestinal tract.

Hodges<sup>151</sup> reports observations on the prophylactic use of sulfadiazine against streptococcal and pneumococcal infections in an Army Air Force Technical School. One gram a day of sulfadiazine was given over a period of several weeks and in some instances 2 Gm on two consecutive days once a week. He concludes that beneficial effects were attained against beta-hemolytic streptococcus infections, scarlet fever, streptococcal sore throat and pneumococcal infections. It is of interest that no serious untoward reactions occurred. No renal symptoms and no depression of the blood cells were reported.

Lee<sup>152</sup> reports the reactions following the massive administration of sulfadiazine to 25,000 men and women as a prophylactic against pneumococcal, streptococcal and meningococcal infections. A total of 2 Gm of sulfadiazine was given. He reports that 0.50 per cent showed "reactions," 0.036 per cent showed "serious reactions."

and 3 patients were "critically ill." No cases of agranulocytosis were observed. It is of interest to note that most of the seriously ill patients gave a history of previous administration of sulfonamide drugs, with reactions. While it is doubtful in our minds that the administration of a single dose of 2 Gm of sulfadiazine would be productive of agranulocytosis, nevertheless it is a remote possibility which cannot be excluded in this report, as blood counts were not given. However, this clinical syndrome did not appear.

The comparative toxicity of sulfadiazine and sulfathiazole in children was studied by Dowrie and Abramson<sup>153</sup>. It is interesting to note that the commonest toxic effect was a fall in the polymorphonuclear cell count below 3,000 cells per cubic millimeter. This occurred in about 40 per cent of the patients in each series, with no great difference between the action of the two drugs. They note that this rate of occurrence of leukopenia is about ten times that reported in any other series, which leads them to believe that the incidence of granulocytopenia is much greater in children than in adults. It is their opinion that a fall in the polymorphonuclear cell count below normal levels does not necessarily indicate that agranulocytosis will develop, and no such complication was observed in their series. In patients for whom use of the drug was continued despite granulocytopenia, the blood counts rose slowly to normal. The authors caution, however, that except in case of the most serious infections the drug should be stopped when there are less than 1,000 polymorphonuclear cells per cubic millimeter. No correlation was discovered between the incidence of granulocytopenia and the daily dose of the drug, the total dose or the length of time of administration of the drug. They conclude that this toxic effect is due to obscure variable factors.

In studying the effects of succinylsulfathiazole on 45 patients, it has been found by Archer and Lehman<sup>154</sup> that the only unfavorable occurrence was a hemorrhagic cutaneous eruption which was seen in a patient who had previously received sulfathiazole. They state that the rash did not progress while the administration of the drug was continued and cleared up promptly when the drug was withheld. There were no changes in the blood picture in any of the patients.

<sup>150</sup> Lederer, M., and Rosenblatt, P. Death During Sulfathiazole Therapy, *J A M A* **119** 8 (May 2) 1942

<sup>151</sup> Hodges, R. G. The Use of Sulfadiazine as a Prophylactic Against Respiratory Diseases, *New England J Med* **231** 817, 1944

<sup>152</sup> Lee, R. V. Reactions Following Mass Administration of Sulfadiazine, *J A M A* **126** 630 (Nov. 4) 1944

<sup>153</sup> Dowrie, J. O., and Abramson, M. H. Comparative Toxicities of Sulfadiazine and Sulfathiazole in Children, *J Pediat* **24** 176, 1944

<sup>154</sup> Archer, H. L., and Lehman, E. P. Clinical and Laboratory Experiences with Succinylsulfathiazole, *Ann Surg* **119** 518, 1944

Page<sup>155</sup> has reported on the treatment of 520 patients with acute bacillary dysentery with sulfaguanidine during a five week period ending June 28, 1943, in Northwest Africa. During this time the patients were given a ten day course of sulfaguanidine, averaging a total dose of 130 Gm. He reports that there were no deaths or serious complications and that close observation of the blood revealed no anemias or leukopenias.

The important practical point concerning the possibility that a person may be sensitive to a number of sulfonamide drugs is discussed by Park<sup>156</sup>. He reviews the literature which suggests that there may be either single or multiple sensitivity to such drugs when they are given internally or as determined by cutaneous tests. The author studied 40 cases of both internal and eczematous allergy by cutaneous tests and with oral medication with various sulfonamide drugs and related compounds, sulfanilic acid and procaine. He concluded that in 60 per cent of the cases the allergy was confined to one sulfonamide drug, whereas in 40 per cent it occurred to multiple sulfonamide drugs and to sulfanilic acid. He claims that the sensitivity of about half the patients who had multiple sensitivity was due to reaction to the sulfonamide radical ( $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2$ ). Of the other half it was to the aminophenyl radical ( $\text{NH}_2\text{C}_6\text{H}_4$ ), reactions also occurring to procaine. No cases were observed in which there was evidence of sensitization to still smaller groups than these.

A case of agranulocytosis following the administration of sulfapyridine is reported by Park, and a discussion of the mechanism responsible for the reduction in the neutrophils is given. After an examination of the reported cases of neutropenia from other drugs, Park states the opinion that all such cases are based on allergic responses. He also believes that other toxic effects of the sulfonamide drugs are probably on the same basis. It is his opinion that as a working rule chemotherapy should not be prolonged beyond the period of one week, since it may induce a dangerous form of drug allergy. Furthermore, most amenable infections respond within a few days, and longer administration is seldom necessary. It is his belief that sensitivity develops gradually, the first indications being a depression of the neutrophils in the blood. Following this there are constitutional symptoms, such as malaise and headache, which may go unnoticed in a patient already ill from the acute

infection. With the complete disappearance of the neutrophils, the alarming syndrome of agranulocytosis suddenly appears. If sulfonamide therapy for longer than one week is necessary, then daily leukocyte counts should be made, and at the first sign of neutropenia the drug should be stopped and its elimination encouraged by promoting diuresis. He is unable to say how long this alleged allergic state persists, but it lasts perhaps for a period of several weeks if it is on the same basis as sulfonamide eruptions. Until this point is cleared up, however, he cautions that a victim of neutropenia requiring a sulfonamide compound subsequently should be given it in ascending doses with extreme caution.

A case of acute and fatal agranulocytosis with toxic dermal lesions produced by the therapeutic use of sulfathiazole in an infant 8 weeks old is reported by Kato, Sherman and Cannon<sup>157</sup>. At the time of this report no other cases of agranulocytosis in infants following sulfathiazole medication had been recorded, although instances of extreme granulocytopenia in children due to other members of the sulfonamide group had been observed. In this case, a total of 4.153 Gm of sulfathiazole was given over a period of five weeks with frequent interruptions. At the end of this time the classic manifestations of agranulocytosis developed, which terminated fatally. These observations were confirmed by autopsy.

A case of a 22 year old white woman in whom agranulocytosis developed after she had received sulfadiazine and who recovered is reported by Meyer<sup>158</sup>. This patient received 44 Gm of sulfathiazole as treatment for osteomyelitis of the terminal phalanx. The drug was discontinued because fever and a rash developed. The white blood cell count at this time was normal. Two days later the patient was given 1 Gm of sulfadiazine every four hours, and after she had received 72 Gm of this drug the white blood cell count was found to be 3,000 per cubic millimeter. A differential count showed 1 per cent segmented forms, 1 per cent stab forms, 3 per cent basophils and 95 per cent lymphocytes. The hemoglobin content was 85 per cent. The lesions of the mucous membranes characteristic of agranulocytosis appeared. Recovery followed the use of pentnucleotide, liver extract, blood transfusion and high intake of vitamin C.

157 Kato, K., Sherman, M. S., and Cannon, P. R. Fatal Agranulocytosis Following Sulfathiazole Therapy. Report of Infant with Toxic Dermatitis, *J. Pediat.* **22**: 432, 1943.

158 Meyer, A. H. Agranulocytosis. Report of Case Caused by Sulfadiazine, *California & West Med.* **60**: 277, 1944.

155 Page, S. G. Sulfaguanidine in Treatment of Acute Bacillary Dysentery. Study of Five Hundred and Twenty Cases, *Virginia M. Monthly* **70**: 561, 1943.

156 Park, R. G. Pathogenesis of Sulfonamide Neutropenia, *Lancet* **1**: 401, 1944.

The case of an 18 year old youth in whom agranulocytosis developed after he had received 31 Gm of sulfadiazine over a period of twenty-eight days because of an infection of the upper respiratory tract is reported by Blue<sup>159</sup>. The drug was discontinued when a sore throat, enlarged lymph nodes, cough and evidence of bronchopneumonia in the right side of the thorax appeared. His white blood cell count was found to be 1,950 per cubic millimeter, with 97 per cent lymphocytes and 3 per cent monocytes. Treatment was with repeated blood transfusions and pentnucleotide. The patient recovered, despite the fact that during the course of his illness he had acute catarrhal fever, lobar pneumonia, agranulocytic angina, acute myocarditis, acute otitis media, cervical adenitis and pyelonephritis.

The case of a patient 25 years of age in whom classic evidences of agranulocytosis developed after the administration of sulfadiazine is reported by Weinberg<sup>160</sup>. After receiving 102 Gm of sulfadiazine orally for a period of twenty days, this patient had a complete absence of granulocytes in the circulating blood and the white blood cell count fell as low as 900 cells per cubic millimeter. The red blood cell count was not affected. With the discontinuance of the drug and administration of liver extract, pentnucleotide and multiple blood transfusions, the patient recovered from this complication but succumbed to subacute bacterial endocarditis, which was superimposed on rheumatic heart disease. It is of interest to note that after the patient recovered from agranulocytosis, sulfathiazole was given over a period of twenty-one days and aminopyrine for an interval of almost two months without a depression in the leukocyte count. Hettig and Sturgis have previously stressed the possible etiologic significance of a vitamin deficiency in agranulocytosis<sup>161</sup>. It is of interest to note that the patient had lost a total of 33 pounds (15 Kg) in weight in four weeks just prior to the onset of the agranulocytosis. There is no indication in the report that the patient had a vitamin deficiency, but the loss of such a large amount of weight suggests this as a possibility.

The first case of agranulocytosis following the administration of sulfamerazine is added to the literature by Favorite, Reiner and London<sup>162</sup>.

The patient was a white man 51 years of age who was given 42 Gm of sulfamerazine over a period of twenty-three days for acute pharyngitis. The white blood cell count dropped as low as 600, and there was at times a total absence of all granulocytes. There were no important changes in the red blood cell count, hemoglobin content or platelets. The patient was treated with pentnucleotide and liver extract in large doses, but the authors properly conclude that it is impossible to say whether its administration influenced the course of the disease favorably. Improvement followed five days after these drugs were first given and six days after the discontinuance of sulfamerazine. As far as we know, no other cases of agranulocytosis have been reported as due to sulfamerazine.

The case of a man aged 42, in whom acute agranulocytosis developed thirteen days after a laparotomy for gastric ulcer was performed, is reported<sup>163</sup>. At the time of the operation 5 Gm of sulfanilamide crystals was scattered along the suture lines and over the area of resection because of presumed contamination. Thirteen days later the white blood cell count was 2,700 per cubic millimeter and there was a decided increase in the number of nonsegmented forms of neutrophilic leukocytes. After an interval of four more days, that is, seventeen days after the operation, the granulocytes had almost disappeared, and they remained noticeably decreased until the patient's death, nineteen days after the operation. The patient received no additional sulfanilamide or any other drugs which might have caused the condition. So far as we are aware, this is the first reported instance in which agranulocytosis has been observed to follow the local or topical application of one of the sulfonamide drugs.

The first case in the literature, as far as we know, of agranulocytosis following the use of sulfaguanidine is reported by Grant<sup>164</sup>. The patient was a 15 year old girl, who was given the drug for the treatment of *Shigella paradysenteriae* Sonne infection. After she received 25.2 Gm, with resultant improvement, the therapy was discontinued for an interval of six days and then resumed on account of a recurrence of symptoms until 15 Gm more had been admin-

159 Blue, J. A. Allergic Agranulocytosis with Complications. Case Report, *Am J M Sc* **207** 453, 1944.

160 Weinberg, H. B. Agranulocytosis Following Sulfadiazine Administration, *J Iowa M Soc* **34** 63, 1944.

161 Hettig, R. A., and Sturgis, C. C. Sulfadiazine Agranulocytosis, *J Michigan M Soc* **42**:959, 1944.

162 Favorite, G. O., Reiner, L., and London, R. Acute Agranulocytosis During Sulfamerazine Therapy, *J Lab & Clin Med* **29** 899, 1944.

163 Arrowsmith, W. R., Binkley, B., and Moore, C. V. Fatal Agranulocytosis Following the Intraperitoneal Implantation of Sulfanilamide Crystals, *Ann Int Med* **21** 323, 1944.

164 Grant, A. Severe Granulocytopenia from Sulfaguanidine, *Brit M J* **1** 557, 1944.

istered. At this time it was discontinued on account of a febrile response. The following day the white blood cell count was found to be 4,100 per cubic millimeter, with 38 per cent neutrophils, a day later the count was 2,000 per cubic millimeter, with only 10 per cent neutrophils. The patient recovered after the discontinuance of the drug and the use of pentnucleotide. The author states that the Medical Research Council Memorandum 1943 b emphasizes the fact that two thirds of the amount of sulfaguanidine administered orally is absorbed before the ileocecal valve is reached. He cites Firor and Poth<sup>165</sup> as stating that the relatively low concentrations of this drug in the blood are due in far greater measure to rapid elimination in the urine than to poor absorption from the intestine. He considers, therefore, that the possibility of agranulocytosis resulting from the administration of sulfaguanidine merits attention.

It is stated by Sherlock and White<sup>166</sup> that the literature contains records of only 18 cases of purpura in association with sulfonamide administration. They give the details of a case as follows. A man aged 52 was treated with sulfapyridine for pneumonia. He received 30 Gm in seven days, after which his temperature fell to normal and the drug was discontinued. On account of a second rise in temperature, he was given 4.5 Gm during the next five days. Fever appeared after each dose of sulfapyridine. Extensive evidences of purpura developed, with bleeding from the nose and gums and the vomiting of blood as well as with a purpuric eruption. The hemoglobin content was 47 per cent, the red blood cell count was 2,500,000 per cubic millimeter, leukocytes 10,000 per cubic millimeter, platelets 150,000 per cubic millimeter, bleeding time thirty-six and one-half minutes, coagulation time twenty-seven minutes and clot retraction in one hour was 19 per cent, whereas the normal is regarded as 44 to 66 per cent. The capillary resistance test by positive pressure method indicated a decided increase in fragility. Sternal marrow showed that megakaryocytes were present (0.4 per cent), and these appeared normal. The patient died, and just before death it was observed that his blood pressure was 260 systolic and 140 diastolic and that the plasma urea content was 214 mg per hundred cubic centimeters. It was considered that the recent hemorrhagic changes in the kidney were re-

sponsible for the impairment of renal function. In addition the authors point out that gastrointestinal hemorrhage could play a part in producing azotemia. It was concluded that the hemorrhagic state in their patient was, therefore, probably the cause rather than the result of the uremia. They emphasize the importance of the capillaries in the pathogenesis of the purpura and state that in the 7 recorded cases of purpura following sulfonamide therapy in which the resistance of the capillaries was tested an extreme fragility was noted. In 4 of the reported cases, including their own, the platelet count, although low, had not been reduced to the level usually associated with bleeding in essential thrombopenic purpura. They state that in the reported cases no member of the sulfonamide group of drugs seemed exempt as a causative agent, and sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine have all been held responsible. The high mortality of this condition, as indicated by a fatal termination in 8 of the 9 cases, makes early recognition essential. In their opinion the first clinical sign is nearly always epistaxis. They believe that adequate transfusion of fresh blood is probably the best type of treatment.

The literature in reference to the occurrence of thrombopenic purpura following sulfonamide therapy is reviewed briefly by Brillinger,<sup>167</sup> and a case report is presented. At the time the article was written he stated that there were 18 cases of thrombopenic purpura following the administration of various sulfonamide drugs reported in the literature. These include cases of purpura following the use of sulfanilamide, azosulfamide, sulfapyridine, sulfathiazole and sulfadiazine. He emphasized particularly that in all but 3 of these cases the purpuric reaction occurred while the drug was being given or at least on the day after it was discontinued. The longest interval between the cessation of use of the drug and the appearance of the purpura was eleven days. Two of the three delayed reactions followed administration of sulfathiazole. His own patient was a healthy man 29 years of age who previously had not been ill. He was treated with 360 grams (23.3 Gm) of sulfathiazole over a period of five days, at which time the use of sulfathiazole was discontinued because of albuminuria with many sulfonamide crystals in the urine. The purpura appeared for the first time on the eighteenth day, some thirteen days after the cessation of the medication. This was accompanied with a high leukocyte count and by a decidedly leukemoid

<sup>165</sup> Firor, W. M., and Poth, E. J. Intestinal Antisepsis, with Special Reference to Sulfamylguanidine, *Ann Surg* **114** 663, 1941.

<sup>166</sup> Sherlock, S., and White, J. C. A Fatal Case of Purpura After Sulphapyridine, *Brit M J* **2** 401, 1944.

<sup>167</sup> Brillinger, H. R. A Case of Delayed Thrombopenic Purpura Following Sulfathiazole Therapy, *J Canada M Serv* **1** 324, 1944.

blood picture. It is stated that the lowest platelet count was 110,000 per cubic millimeter, the bleeding time was three minutes and the clotting time eleven minutes. The patient recovered completely after two small transfusions of citrated blood.

Meyer<sup>168</sup> states that in the literature there are 2 previous reports of thrombopenic purpura developing from the use of sulfadiazine. These are reported by Kracke and Townsend<sup>169</sup> and by Gorham and others<sup>170</sup>. The patient reported on by Meyer was a 7 year old boy who became ill with chickenpox and in whom impetiginous lesions subsequently developed. Sulfathiazole ointment for local application was prescribed, and sulfadiazine was given amounting to a total of 4.5 Gm in one and one-half days, at which time purpuric spots were noted about the knees and buttocks. An additional 3 Gm was administered in two and one-half days, at the end of which time the urine became bloody, after a total of 9 Gm had been given, the hematuria became so pronounced that the child was hospitalized. There were purpuric spots over the entire body. The hemoglobin content was 23 per cent with 1,433,000 red blood cells per cubic millimeter, platelets 20,000 per cubic millimeter and white blood cells 23,850 per cubic millimeter, with 85 per cent segmented neutrophils. Bleeding time was forty-five minutes and the clotting time six minutes, with little retraction after eighteen hours. The reaction to the tourniquet test was strongly positive. The urine was grossly bloody. The patient was given transfusions with a total of 1,750 cc of blood in units of 300 cc. Two weeks after his admission to the hospital the bleeding time was one and one-half minutes, the platelet count 139,000 per cubic millimeter, the hemoglobin content 89 per cent and the urine normal. The patient made a complete recovery.

Reference is made by Latven and Welch<sup>171</sup> to the previous work of Richardson,<sup>172</sup> who reported

that in mice hemolytic anemia of variable intensity develops within a period of two weeks when sulfanilamide, sulfaguanidine, sulfapyridine or sulfathiazole is incorporated in a stock ration. The potentiality of each of these sulfonamide compounds for the production of hemolytic anemia was related by Richardson to the concentration of the compound within the erythrocytes. Latven and Welch have studied the hemolytic anemia-producing properties of sulfapyridine, sulfamerazine and sulfadiazine, which have been evaluated in mice. This evaluation has been accomplished by determining the percentage incidence of anemia produced by various concentrations of sulfonamide compounds in the blood. They found that the concentration of sulfonamide compounds in the blood necessary to produce a 50 per cent incidence of anemia in mice was as follows: with sulfapyridine 2.8 mg, with sulfadiazine 33 mg and with sulfamerazine 31 mg per hundred cubic centimeters. They conclude that a large number of cases will be required to prove conclusively that in human beings, as in mice, sulfadiazine is decidedly less productive of hemolytic anemia than are sulfathiazole and sulfapyridine.

A case of acute hemolytic anemia following the administration of 39 Gm of sulfadiazine to a patient with bronchopneumonia for a period of nine days is reported by Layne and Schemm<sup>173</sup>. The anemia in this patient became very severe, as the hemoglobin content was 3.75 Gm per hundred cubic centimeters (24 per cent) and the red blood cell count 1,270,000 per cubic millimeter. The authors point out that improvement in the patient's anemia occurred coincidentally with the administration of 90 units of liver extract on two successive days. They recognize that this may have played no role in the patient's recovery. Some evidence has been offered, however, to suggest that liver extract is effective in correcting the granulocytopenia and the anemia in rats fed various sulfonamide drugs. They conclude that this form of therapy may have contributed to the patient's recovery.

#### AGRANULOCYTOSIS DUE TO VARIOUS CAUSES

*Thiouracil*—In a comprehensive article on the use of thiouracil in the treatment of hyper-

168 Meyer, A. H. Thrombocytopenic Purpura Case Caused by Sulfadiazine, *California & West Med* 60:98, 1944.

169 Kracke, R. R., and Townsend, E. W. The Effect of Sulfonamide Drugs on the Blood Platelets. Report of Two Cases of Thrombopenic Purpura and Experimental Studies on Patients Receiving Sulfonamide Drugs, *J. A. M. A.* 122:168 (May 15) 1943.

170 Gorham, L. W., Propp, S., Schwind, J. L., and Climenko, D. R. Thrombocytopenic Purpura Caused by Sulfonamide Drugs. A Report of Three Cases, *Am. J. M. Sc.* 205:246, 1943.

171 Latven, A. R., and Welch, A. D. Sulfamerazine (2-Sulfanilamido-4-Methylpyrimidine). III. Comparative Activity of Sulfamerazine, Sulfadiazine and Sulfapyridine in Production of Hemolytic Anemia in Mouse, *J. Pharmacol. & Exper. Therap.* 81:301, 1944.

172 Richardson, A. P. Comparative Effects of Sulfonamide Compounds as to Anemia and Cyanosis, *J. Pharmacol. & Exper. Therap.* 72:99, 1941.

173 Layne, J. A., and Schemm, F. R. Acute Macrocytic Hemolytic Anemia Occurring Following Administration of Sulfadiazine, *J. Lab. & Clin. Med.* 29:347, 1944.

thyroidism, Astwood<sup>174</sup> discusses the various toxic complications which may develop during the course of the therapy. According to him the most serious one is agranulocytosis, and he reports 2 cases in detail. In 1 the patient was given the excessive dose of 2 Gm daily and recovered after the omission of the drug. It is of interest that the same patient subsequently experienced a febrile reaction to sulfathiazole given while he had a scarlatiniform eruption following the administration of phenobarbital. Astwood suggests, therefore, the possibility that persons in whom allergic reactions readily develop are more likely to become sensitized to thiouracil. Another patient, who had received 0.6 Gm of thiouracil for sixty-two days and 0.3 Gm for an additional thirty-one days, had a streptococcal infection of the finger on the eighty-fifth day but did not return to the clinic for a week. In that interval she had received 4 Gm of sulfamerazine daily for three days and 3 Gm daily thereafter. When first determined, the total white blood cell count was 2,000, of which 5 per cent were granulocytes. Discontinuance of both the thiouracil and the sulfonamide therapy, with local treatment of the digital infection and of the ulcerative stomatitis and pharyngitis, was followed by complete recovery. The differential count became normal within ten days. It is impossible in this case to determine to what degree thiouracil, sulfamerazine and the infection may each have contributed to the leukopenia. Astwood also states that had the patient been under more careful observation the complication might have been detected before reaching an alarming degree of severity. A number of instances of leukopenia of varying degree occurred in the cases in his series. Although the total leukocyte count fell to 3,000 or 4,000 per cubic millimeter or less on some occasions, it subsequently rose in spite of the fact that the drug was continued. In Astwood's opinion "it is uncertain" whether or not all these mild leukopenias are due to the drug. He states that about 10 per cent of all patients who receive thiouracil will have toxic manifestations, either febrile or in association with a leukopenia. The best indications of impending danger of toxic reactions, he believes, are the subjective sensations of the patient and the body temperature. Frequent leukocyte counts, while helpful, apparently are not as reliable as clinical symptoms in indicating the early onset of serious complications. Serious side effects can probably be avoided if the patients are instructed

174 Astwood, E. B. Thiouracil Treatment in Hyperthyroidism, *J Clin Endocrinol* 4: 229, 1944.

to seek medical advice as soon as abnormal symptoms are experienced.

Williams and Clute<sup>175</sup> reported the effect of thiouracil on 72 patients, including a continuation of the study of 9 patients previously reported by Williams and Bissell.<sup>176</sup> The most serious complication encountered was leukopenia with agranulocytosis, which occurred in 1 patient. This occurred at the end of six weeks of treatment, during which time the patient had received 0.6 Gm of thiouracil daily for the first two weeks, 0.4 Gm daily for the next two weeks and 0.2 Gm daily for the last two weeks. The leukocyte count was determined when the patient complained of an infected finger and fever. Treatment consisted of pentnucleotide and large doses of crude liver extract. Complete recovery occurred, although for a period of seven days only a few granulocytes were present in the circulating blood. In another case the white blood cell count dropped to 3,200 with 20 per cent granulocytes only a few days after treatment with thiouracil was begun. Despite continued therapy the white blood cell count returned to normal and the granulocytes rose 50 per cent. Subsequently the patient took thiouracil for more than six months and remained in good health. Leukopenia and granulocytopenia were seen in some other cases, but the incidence was apparently no greater than that observed in untreated thyrotoxic patients. These authors conclude that of the various complications encountered thus far the only one to cause appreciable concern is agranulocytosis.

In the review of the action of antithyroid drugs, with particular reference to thiouracil, Williams<sup>177</sup> has this to say in regard to the toxic actions of thiouracil. According to him, such untoward effects are to be anticipated in about 10 per cent of the patients, most of the complications have appeared in the first five weeks of treatment. These have consisted of fever, morbilliform rash, urticaria, arthritis, vomiting, diarrhea, enlargement of the submaxillary salivary glands, edema of the legs, lymphadenopathy, leukopenia and agranulocytosis. In his opinion, the last of these is the only serious toxic reaction. At the time his article was written only 2 cases of toxic reaction to thiouracil with death due to agranulocytosis had been reported, but Williams states that he has knowl-

175 Williams, R. H., and Clute, H. M. Thiouracil in the Treatment of Thyrotoxicosis, *New England J Med* 230: 657, 1944.

176 Williams, R. H., and Bissell, G. W. Thiouracil in the Treatment of Thyrotoxicosis, *New England J Med* 229: 97, 1943.

177 Williams, R. H. Antithyroid Drugs, with Particular Reference to Thiouracil, *Arch Int Med* 74: 479 (Dec) 1944.

edge of several other cases which have not been published. Of 170 patients he has treated, 2 have had agranulocytosis. Undoubtedly other patients do not have the outspoken syndrome of agranulocytosis but do have an important leukopenia, which is an indication that the patient's treatment should be stopped or continued under careful supervision. According to Williams, except for fever, arthritis and leukopenia, the complications have been observed to disappear when the dosage of thiouracil was reduced.

The case of a 44 year old woman with exophthalmic goiter of one year's duration who received thiourea and in whom purpura developed is reported by Newcomb and Deane.<sup>178</sup> Thiourea in a dosage of 1 Gm three times a day was given for three weeks. Ten days after the use of the drug had been started, the signs of hyperthyroidism began to recede, at which time the dosage of thiourea was reduced to 1 Gm twice a day for a week and then 1 Gm daily. Two weeks after the drug had been started, the leukocyte count was 9,200 per cubic millimeter, with 70 per cent granulocytes and a normal differential count. After a total of 83 Gm had been given, namely, five weeks after the beginning of treatment, epistaxis and a generalized purpura developed, with ecchymoses and purpuric spots on the buccal mucous membrane. The administration of thiourea was immediately stopped. The following day the ecchymoses became more numerous, and there was bleeding from the gums. There were a normal red blood cell count and hemoglobin content. The white blood cell count was 4,100 per cubic millimeter with 24 per cent granulocytes, the platelets were 18,000 per cubic millimeter. The bleeding time was greatly prolonged, and at the end of four hours bleeding from the venipuncture wound showed no signs of ceasing. The coagulation time was normal. Sternal puncture revealed no important changes except that the platelets were scanty and only 2 megakaryocytes were seen. The white blood cell count fell to 3,700 per cubic millimeter, with 16 per cent polymorphonuclear neutrophils, and there were 9,000 platelets per cubic millimeter. She was given 500 cc of fresh whole blood, and all bleeding promptly ceased. A few doses of pentnucleotide were given. The patient made a complete recovery, and twelve days after the appearance of purpura the leukocyte count was 6,200, with 36 per cent granulocytes and 67,000 platelets. The report of this case is important because not only granulocy-

topenia but also thrombopenic purpura developed.

McGavack and his associates<sup>179</sup> reviewed the toxic reactions due to thiouracil in 135 patients with toxic goiter. In this group 2 had agranulocytosis and recovered. In addition, a transient leukopenia appeared in 3 patients. One of the patients in whom agranulocytosis developed was a 50 year old white woman who received 0.5 Gm of thiouracil daily for forty-one days. At this time fever, sore throat, gingivitis, headaches and enlargement and tenderness of the cervical lymph nodes developed. The blood count taken at this time showed 3,500 white blood cells per cubic millimeter, with 97 per cent lymphocytes. With cessation of the use of the drug and with the administration of several blood transfusions, recovery was complete. In their opinion it would appear that omission of the drug without any recourse to transfusions would have adequately relieved her condition. In 3 of the patients observed by this group there were decreases in the white blood cells to 3,500, 4,500 and 2,500 per cubic millimeter, and in the percentage of polymorphonuclear leukocytes to 41, 32 and 48, respectively. The blood counts returned to normal without a change in the treatment of any of these 3 patients. It is questionable, therefore, in their opinion whether one should regard these responses as pathologic or as physiologic, and it is difficult to be sure whether leukopenia with lymphocytosis can be considered as a toxic phenomenon. In any event, it hardly warrants complete cessation of therapy. A more satisfactory course would be to consider such responses as an indication for temporary or permanent decrease in the size of the dose employed. From our experience, it would seem that leukopenia occurs more commonly in patients who are receiving thiouracil than would be indicated by the reports in the literature. In our group of patients for whom leukocyte counts were determined every other day, a moderate leukopenia without evidence of agranulocytosis occurred in a great percentage of patients. In almost all instances, however, with continuation of the therapy or its interruption for only one or two days, there was a return of the white blood cell count to normal. Until knowledge is more complete on this subject, however, any significant decrease in the white blood cell count with a diminution in the number of polymorphonuclear leuko-

<sup>178</sup> Newcomb, P. B., and Deane, E. W. Thiourea Causing Granulopenia and Thrombopenia, *Lancet* 1: 179, 1944.

<sup>179</sup> McGavack, T. H., Gerl, A. J., Vogel, M., and Schwimmer, D. Treatment of Twenty-Six Thyrotoxic Patients with Thiouracil and Review of Toxic Reactions in All (135) Reported Cases, *J. Clin. Endocrinol.* 4: 249, 1944.

cytes is an indication to observe the patient with extreme care

It is reported by Kahn and Stock<sup>180</sup> that as far as can be determined their case is the first in which death occurred from agranulocytosis attributable to thiouracil. The patient was a 62 year old woman with severe and uncontrolled diabetes and a diffuse toxic goiter, with a basal metabolic rate of  $\pm$  65 per cent. The diabetes was well controlled, and the patient was given thiouracil, 0.6 Gm daily for forty-four days and then 0.4 Gm for eight days. A total dose of 30.8 Gm was given in fifty-four days. On the fifty-first day of treatment, the body temperature was elevated to 101.4 F and the patient complained of a sore throat. Within twenty-four hours the white blood cell count was found to be 1,100 per cubic millimeter, with 2 per cent granulocytes. The patient died five days after the onset of the agranulocytosis, despite all forms of therapy, including blood transfusions, use of crude liver extract, pentose nucleotide, extract of yellow bone marrow and penicillin. It was assumed that the thiouracil was the cause of the toxic hepatitis which was also present as well as of the agranulocytosis. The severe diabetes mellitus was regarded as a contributory factor in the death of the patient.

David Haller states,<sup>181</sup> "Thiouracil is a dangerous drug, and at least half a dozen fatal cases of agranulocytosis have been described following its use [no reference or further details are given], and only this week I conducted a necropsy upon such a case, the inquest resulting in a verdict of misadventure following the administration of thiouracil." In the author's opinion, the drug should be given only under the strictest control in a hospital.

In a general article on the use of thiouracil in the preparation of patients with hyperthyroidism for thyroidectomy, Moore and his associates<sup>182</sup> state that in their opinion thiouracil exhibits a toxicity similar to that of the sulfonamide drugs. Among 52 patients treated up to the time the article was written, they observed 2 with leukopenia, 4 with oral infections possibly related to the medication and 1 with a generalized lymphadenopathy which cleared after discontinuance of the drug. In the patients with leukopenia the white blood cell count was about

2,500 per cubic millimeter. The polymorphonuclear leukocytes were never below 30 per cent. In treatment of 1 patient the drug was continued until the count was normal, in treatment of the other the use of the drug was stopped. In no case, however, in the experience of these observers, has any toxic manifestation either prevented or complicated operative removal of the gland.

St Johnston<sup>183</sup> reports on 3 patients with toxic goiter treated with thiourea in doses of 3 Gm daily for periods of seven to eight days who had temperatures of 100.4 to 101 F, with palpable enlargement of the spleen, a fall in the white blood cell count with monocytosis and a maculopapular eruption. There was no pronounced drop in the white blood cell count in any instance, the lowest being 4,600 white blood cells per cubic millimeter, with 51 per cent polymorphonuclear leukocytes. The enlargement of the spleen was unexplained.

Rubinstein<sup>184</sup> reports the case of a woman 47 years old, who suffered from carcinoma of the thyroid gland. She was given thiouracil in a dosage of 0.2 Gm four times a day for approximately fifteen weeks. It is of interest to note that the thyroid nodes became somewhat diminished in size and softer in the supraclavicular region. After a period of fifteen weeks the white blood cell count was observed to be 1,700 per cubic millimeter and a few days later it fell to 750. At this time there were 4 per cent myelocytes and 10 per cent neutrophils. Studies of the bone marrow showed an arrested maturation associated with hypoplasia of the myeloid elements of the bone marrow, which was taken as the explanation for agranulocytosis of the peripheral blood. After the use of the drug was discontinued, a complete hematologic recovery followed. A return to normal of the bone marrow preceded that of the peripheral blood.

A patient observed by Linsell<sup>185</sup> received continuous thiouracil therapy for four months, with a daily dose of 1 Gm for one month and 0.2 Gm daily subsequently. The neutropenia developed after ten weeks of treatment, when the patient had taken approximately 44 Gm. At this time she had an acute febrile attack with some ulceration of the mouth and sore throat, which cleared up entirely without treatment within six days. After twelve weeks of addi-

180 Kahn, J, and Stock, R P. Fatal Agranulocytosis Resulting from Thiouracil, *J A M A* **126** 358 (Oct 7) 1944.

181 Haller, D. Letter to *Brit M J* **1** 382, 1944.

182 Moore, F D, Sweeney, D N, Jr, Cope, O, Rawson, R W, and Means, J H. Use of Thiouracil in Preparation of Patients with Hyperthyroidism for Thyroidectomy, *Ann Surg* **120** 152, 1944.

183 St Johnston, C R. Toxic Reaction to Thiourea. Report on Three Cases, *Lancet* **2** 42, 1944.

184 Rubinstein, M A. Agranulocytosis Following Thiouracil Administration, *Am J Clin Path* **14** 540, 1944.

185 Linsell, D. Agranulocytosis After Use of Thiouracil, *Brit M J* **2** 597, 1944.

tional treatment with thiouracil during which time she took 48 Gm, she had a much severer febrile attack and was admitted to the hospital for observation. The classic signs of agranulocytosis were present, and, in addition, there was a severe conjunctivitis of the left eye with cellulitis spreading into the orbital tissue. At this time the patient had a white blood cell count of 1,200 per cubic millimeter, and "an occasional degenerate polymorphonuclear cell" was seen in the peripheral blood. Recovery was rapid after the administration of thiouracil was discontinued, although the author attributes some improvement to repeated transfusions of fresh blood. In addition, the patient received pentnucleotide and ascorbic acid.

It is reported by Welshman<sup>186</sup> that thiouracil had been employed in the treatment of 2 patients with thyrotoxicosis and "in both the total white cell count fell to about 2,200 per cubic millimeter with depression of the polymorphs." With discontinuance of the use of the drug, the white cell count rose to 10,000 in five days. Thyroidectomy was performed, and both patients made an uneventful recovery. It was suggested that the drug should be employed with caution and should be used only when there are facilities for making frequent white cell counts.

A study was made of the various tissues of rats after they had received a relatively large amount of thiouracil. Microscopic examination of the bone marrow of approximately 50 rats revealed no definite abnormalities. They had been treated for from seven to ninety days. A few studies were made of the circulating blood obtained from the heart. In several instances the white blood cell count was low (the lowest was 3,600 per cubic millimeter), but the average was 9,000 per cubic millimeter.

Favorable results are reported by Reveno<sup>187</sup> in the treatment of 9 patients. For 6 the results were good, for 3 they were not so satisfactory for various reasons, such as lack of cooperation. No instance of agranulocytosis or anemia occurred.

In treating 11 patients with severe hyperthyroidism with 0.6 Gm of thiouracil daily, Bartels<sup>188</sup> did not observe any toxic effects from the drug. According to him, the white blood cell counts were carefully observed during the course of treatment but no change occurred.

Gabrilove and Kert<sup>189</sup> report the treatment of 9 patients with thiouracil and observed that 3 exhibited manifestations of sensitivity to the drug. In 1 there were a febrile rise and a moderate generalized lymphadenopathy, suggesting that the patient had infectious mononucleosis, but there were a normal hemogram and a negative heterophile reaction of the blood. The second patient exhibited fever and dermatitis. In the third patient, a woman 47 years of age, leukopenia developed with a white blood cell count of 2,650 per cubic millimeter and a differential count of 59 per cent segmented polymorphonuclear neutrophils, 4 per cent non-segmented polymorphonuclear leukocytes, 28 per cent lymphocytes, 4 per cent monocytes and 5 per cent eosinophils. This occurred after the patient had been given 1 Gm of thiouracil daily in five divided doses for a period of sixteen days. The use of the drug was stopped, and the patient was then prepared for subtotal thyroidectomy by administration of iodine. She recovered without further complications.

Paschkis and his associates<sup>190</sup> found no toxic manifestations in the blood of 6 patients with thyrotoxicosis who received thiourea. Among the 15 patients with thyrotoxicosis who received thiouracil, toxic manifestations, including leukopenia (2,500 cells per cubic millimeter) developed in 1. This condition became apparent after an infection of the upper respiratory tract which developed after eight months of treatment. The leukocyte count returned to normal, and the rash disappeared three days after the drug was discontinued. Forty-eight hours after treatment was resumed, the leukocyte count fell again but the rash did not reappear. This patient was given 1 Gm of thiouracil for the most part but at times received as much as 2 Gm a day.

The case of a Negro man aged 40, with exophthalmic goiter, in whom agranulocytosis developed after the use of thiouracil, is reported by Meyer<sup>191</sup>. After the patient had received a total of 40.8 Gm of thiouracil in fifty-five days in doses of 1 to 2 Gm, there were a severe chill, a sore throat and a rise in temperature to 104 F. The white blood cell count was 2,000 per cubic millimeter, with 19 per cent segmented neutrophils, 3 per cent juvenile forms and 71 per cent lymphocytes. Recovery followed.

189 Gabrielove, J. L., and Kert, M. J. Sensitivity to Thiouracil. Report of Three Cases, *J. A. M. A.* **124** 504 (Feb 19) 1944.

190 Paschkis, K. E., Cantarow, A., Rakoff, A. E., Walkling, A. A., and Tourish, W. J. Thiourea and Thiouracil in Treatment of Thyrotoxicosis, *J. Clin. Endocrinol.* **4** 179, 1944.

191 Meyer, A. H. Granulocytopenia. A Case Caused by Thiouracil, *California & West Med.* **61** 54 1944.

186 Welshman, B. C. Effect of Thiouracil on the White Cells, Letter to the Editor, *Lancet* **1** 195, 1944.

187 Reveno, W. S. Thyrotoxicosis Treated with Thiouracil, *J. A. M. A.* **126** 153 (Sept 16) 1944.

188 Bartels, E. C. Thiouracil Its Use in the Pre-operative Management of Severe Hyperthyroidism, Preliminary Report, *J. A. M. A.* **125** 24 (May 6) 1944.

the discontinuance of the use of thiouracil and the administration of pentnucleotide and liver extract

*Miscellaneous Agents*—A review of the literature and general clinical observations on agranulocytic angina is given by Copley<sup>192</sup> In this he reports that in the state of Virginia in the past eight years there have been 36 cases of agranulocytic angina which have been reported There were two peaks in these years, one being in 1937, when there were 12 cases, and one in 1940, when there were 10 Three of the 18 deaths since 1930 were due to one of the sulfonamide drugs, according to replies sent by physicians reporting these deaths One fatal case followed the administration of 108 Gm of sulfadiazine over a period of twenty days One patient, a man aged 54, in our opinion did not have agranulocytic angina The patient had taken aminopyrine eleven months before the acute onset, which was preceded by a prodromal period of ill health He was treated with the recommended therapeutic measures, namely, pentnucleotide, blood transfusions and liver extract administered parenterally, and lived three years and eight months It is much more likely, in our opinion, that this patient died of subleukemic leukemia

A comprehensive review on the subject of agranulocytosis and neutropenia is presented by Rodríguez<sup>193</sup>

The rarity of blood dyscrasias following injections of the arsphenamine drugs is emphasized by Ferguson<sup>194</sup> He states that in the United States Navy over a million injections of such drugs were given between the years 1925 and 1938 with only 24 resultant blood dyscrasias, which gives an incidence of roughly 1 in 50,000 He reports on 6 patients with hematologic disorders after treatment with neo-arsphenamine For the first 5 a diagnosis of agranulocytosis was made because the changes were largely limited to a reduction or complete disappearance of the granulocytes in the circulating blood In the sixth patient, however, there was a moderate reduction in the red blood cells, to 4,100,000 per cubic millimeter, with a hemoglobin content of 72 per cent The total white blood cell count was 1,200 per cubic millimeter, with 4 per cent polymorphonuclear

leukocytes, and the blood platelets were 33,600 per cubic millimeter Ferguson classified the illness of the sixth patient as acute aplastic anemia because all elements of the bone marrow were affected The first 5 patients reported on, that is, those with agranulocytosis, received an average of five injections of arsenic with an average dose of 2.1 Gm In the illness classified as aplastic anemia, the damage to the bone marrow was regarded as more extensive, as postmortem studies showed that the megakaryocytes and the precursors of the red blood cells were affected In this patient symptoms did not begin until six or seven weeks after the beginning of antisyphilitic treatment The author believes that in classifying the blood dyscrasias following arsphenamine simple thrombopenia should be grouped separately from the other dyscrasias which are due to involvement of the bone marrow It is thought by this observer that an increased absolute number of monocytes, as found in 3 of the patients with agranulocytosis who recovered, was a favorable prognostic sign This has previously been reported, but there is some difference of opinion as to how reliable it is from the standpoint of prognosis In the cases of agranulocytosis, examination of the bone marrow by sternal puncture and at necropsy showed evidence of arrest of maturation similar to that found in cases of so-called idiopathic agranulocytosis In the opinion of this observer pentnucleotide therapy "appears" to be effective in treatment of agranulocytosis provided treatment is not too long delayed

Two cases of agranulocytosis are reported by Lana Martínez<sup>195</sup> The first is that of a man 28 years old, who was treated for syphilis for about two years with arsphenamine, bismuth and mercury Fever, malaise and increasing fatigue developed, at which time the blood was examined and the white blood cell count was found to be 5,300 per cubic millimeter, with no neutrophils There were 25 per cent lymphocytes present and 75 per cent monocytes The antisyphilitic medication was discontinued, and ascorbic acid was administered Slow improvement followed, and one month later the blood was normal The second case is that of a man 26 years old with syphilis and a gonococcal infection of the urethra He was treated with arsphenamine and sulfonamide drugs, the latter in doses of 3 Gm daily After a few days fever, chills and malaise developed Examination of the blood showed the white blood cell count

192 Copley, E. L. Agranulocytic Angina—a Drug Hazard, Virginia M. Monthly **71** 416, 1944

193 Rodríguez y Rodríguez, A. Sobre la agranulocitosis o neutropenia, Medicina, Madrid (pt II) **12** 491, 1944

194 Ferguson, J. W. Agranulocytosis and Aplastic Anemia After Arsphenamines. Report of Six Cases, Lancet **1** 334, 1944

195 Lana Martínez, F. Dos casos de agranulocitosis, Med. españ. **4** 383, 1940

to be 4,600 per cubic millimeter, with no neutrophils. With the discontinuance of the medication and administration of ascorbic acid the patient improved, and one week later the blood was normal. In neither of the cases were there lesions of the mouth or throat.

A case was reported by Oppikofer<sup>196</sup> of a man 33 years old in whom the classic picture of agranulocytosis developed after the use of several drugs, including aminopyrine. The white blood cell count fell to 5,050 per cubic millimeter, with no granulocytes present in the peripheral blood. The patient was treated with "Nucleotrat" intramuscularly, 10 cc twice daily. He was also given "a number" of blood transfusions. Recovery followed. A brief discussion of the clinical picture of agranulocytosis is given.

A case is reported by Estol Baleztena<sup>197</sup> of a child 10 years of age who had previously suffered from pulmonary tuberculosis. Two injections a week of a gold preparation (*Sonocisina*) were given in a dose of 0.025 Gm for each injection. After five injections, fever, sore throat and agranulocytosis developed. Recovery followed symptomatic treatment.

A case of agranulocytosis developing in a woman aged 45, in whom the white blood cell count fell to a minimum of 900 per cubic millimeter, with 10 per cent granulocytes, is reported by Rawls<sup>198</sup>. This patient had rheumatoid arthritis and had taken acetylsalicylic acid, acetophenetidin and neocinchophen at various intervals without any signs of toxicity. Agranulocytosis developed after she was said to have taken 7½ grains (0.48 Gm) of cinchophen three times a day and 1 mg of menadione (2-methyl-1,4 naphthoquinone, synthetic vitamin K) three times a day for six days. It is "assumed" by the author that the synthetic vitamin K radical may have been responsible for this condition, as it contains the quinone radical, which, in his opinion, might produce agranulocytosis. Certainly the evidence is not clear in this case that the agranulocytosis was due to this particular drug.

A familial type of malignant chronic granulocytopenia is described by Béguez César<sup>199</sup>. This

condition is characterized by albinism, indeterminate feverish states, nystagmus, leukopenia, granulocytopenia and lymphomonocytosis. The author considers it to be a familial disease. According to him it has the characteristics of a recessive mendelian trait. Of 13 brothers studied by him, 4 suffered from the condition. He concludes that of the 9 living brothers a number will transmit the disease while others will not.

Experiments were performed by Staub and Bucher<sup>200</sup> in which they injected solutions of glycogen into rabbits and concluded that the leukopenia which resulted was proportionate to the size of the glycogen molecules. When a large molecule solution was injected the leukopenia was greater than that produced by one containing small molecules. They conclude that leukopenia is dependent to a certain extent on the physical state of the molecules of the injected substance.

The case of a woman aged 26 is reported by Barling<sup>201</sup> in which the unusual feature was that for twelve years the patient had complained of ulcers in the mouth recurring at regular intervals of three to four weeks. It was discovered by Barling that the appearance of the ulcers was associated with a pronounced reduction in the total white blood cell count. On one occasion it was 2,600 per cubic millimeter, with 44 per cent polymorphonuclear cells. The ulcers were shallow and appeared on the tongue and inside the mouth and were sufficiently painful to make mastication difficult. There was no response noted to any form of treatment. F. Parks Weber, in discussing this case refers to 1 previously reported by D. Embleton<sup>202</sup> under the title "Rhythmical Neutropenia with Recurrent Buccal Ulceration" in a woman aged 43. Apparently these cases are similar to those which have been observed in this country and are regarded as instances of a recurrent stomatitis associated with pronounced granulocytopenia. The cause of this condition is not known, but in our minds the possibility that it is due to a filtrable virus should be considered.

*Possible Relation of Folic Acid to Agranulocytosis*—It has been suggested by Goldsmith,

196 Oppikofer, E. K. Ueber Otitis und Rhinitis necroticans agranulocytotica, *Schweiz med Wchnschr* 73 107, 1943.

197 Estol Baleztena, M. M. Agranulocitosis secundaria a un tratamiento de sales de oro, *Prensa med argent* 31 85, 1944.

198 Rawls, W. B. Agranulocytopenia in Patient Receiving Cinchophen and Synthetic Vitamin K, *New York State J Med* 44 626, 1944.

199 Béguez César, A. Neutropenia crónica maligna familiar con granulaciones atípicas de los leucocitos, *Boletín Soc cubana de pediat* 15 900, 1943.

200 Staub, H., and Bucher, K. Zum Mechanismus der Leukopenia nach i. v. Glykogenzufuhr, Abhängigkeit der Leukopenie von der Grösse der Makromolekel, *Schweiz med Wchnschr* 73 904, 1943.

201 Barling, B. Three and a Half Years' Treatment with Sulphapyridine in Case of Dermatitis Herpetiformis, *Lancet* 1 503, 1944.

202 Embleton, D. Rhythmical Neutropenia with Recurrent Buccal Ulceration, *Proc Roy Soc Med* 30 980, 1937.

Gordon, Finkelstein and Charipper<sup>203</sup> that since the granulocytopenia produced in rats by sulfonamide compounds can be corrected by liver<sup>204</sup> it appeared logical that liver might have the same effect on the thiourea-induced neutropenia occurring in human beings. The experiments of Goldsmith and his associates were performed as follows. Adult male rats were fed a standard laboratory ration containing 0.5 per cent thiourea for fifty-eight days. Six animals of another group were treated similarly but in addition received 5 per cent of solubilized liver incorporated into the ration. The most striking hematologic change in those animals receiving only thiourea and the stock ration was the pronounced neutrophilic granulocytopenia, which became progressively more severe. It was clearly demonstrated in the second group of rats, however, that the administration of liver almost completely prevents the development of the neutropenia. It is strongly suggested, therefore, that the granulocytopenia induced by the administration of either the sulfonamide compounds or thiourea may be prevented by feeding liver. A norite eluate fraction of liver has been found to alleviate the leukopenia in monkeys maintained on a synthetic diet by Waisman and Elvehjem,<sup>205</sup> and these observers have proposed that folic acid is the active agent in this liver fraction. It appears logical, therefore, to use either folic acid or liver in the prevention and treatment of the granulocytopenia resulting from the administration of thiourea compounds in hyperthyroid patients.

It is stated by Endicott, Kornberg and Daft<sup>206</sup> that in a previous report from the United States Public Health Laboratory the lesions found in rats fed sulfaguanidine in purified diets were described. One of these lesions was agranulocytic aplasia of the bone marrow. During the past year, studies have been made of sulfathiazole, sulfadiazine, sulfanilamide, sulfapyrazine,

sulfamerazine and acetylsulfadiazine given rats in purified diets. Among the pathologic changes noted was a depletion of mature granulocytes in the bone marrow with or without an increase in nucleated red blood cells. It is interesting to note that hyperplasia of the marrow was found regularly in rats recovering from granulocytopenia thus induced and that recovery followed treatment with certain liver concentrates.

Totter and his associates<sup>207</sup> have observed that the rhesus monkey requires a water-soluble substance or substances to prevent leukopenia, anemia, diarrhea, lesions of the mouth and colon and eventual death. This factor, for which the term vitamin M was suggested, was shown to be distinct from thiamine, riboflavin and nicotinic acid. Evidence is presented to indicate that the distribution of the factors stimulating growth of *Streptococcus lactis* R (folic acid) is different from that of factors stimulating growth of vitamin M. Furthermore, they showed that pantothenic acid, choline, paraaminobenzoic acid, pyridoxine and inositol do not prevent nutritional cytopenia in the monkey. They found that the treatment of the cytopenic monkeys with synthetic xanthopterin was followed by a reticulocyte response and an increase in the red and white blood cell count. They concluded that the evidence suggests that xanthopterin or some closely allied substance may be required by the monkey for normal hemocytopoiesis. However, it seems probable that unidentified substances may also be necessary.

It is reported by Wright and Welch<sup>208</sup> that the feeding of a highly purified diet adequate in those members of the vitamin B complex required for the production of excellent growth in rats caused a decided reduction in the hepatic stores of folic acid and biotin compared to the amounts of these factors found in the livers of animals maintained on stock rations. The hepatic storage of these factors was further reduced by the incorporation of succinylsulfathiazole into such synthetic rations. It is important to note that there was no impairment in the storage of riboflavin and of nicotinic acid. These experiments are of interest to us because the findings are in accord with the hypothesis that folic acid deficiency may contribute to the development of agranulocytosis. This is due to the fact that

203 Goldsmith, E. D., Gordon, A. S., Finkelstein, G., and Charipper, H. A. Suggested Therapy for Prevention of Granulocytopenia Induced by Thiourea, *J. A. M. A.* **125** 847 (July 22) 1944.

204 Spicer, S. S., Daft, F. S., Sebrell, W. H., and Ashburn, L. L. Prevention and Treatment of Agranulocytosis and Leukopenia in Rats Given Sulfanilylguanidine or Succinyl Sulfathiazole in Purified Diets, *Pub. Health Rep.* **57** 1559, 1942. Kornberg, A., Daft, F. S., and Sebrell, W. H. Production and Treatment of Granulocytopenia and Anemia in Rats Fed Sulfonamides in Purified Diets, *Science* **98** 20, 1943.

205 Waisman, H. A., and Elvehjem, C. A. Role of Biotin and "Folic Acid" in Nutrition of Rhesus Monkey, *J. Nutrition* **26** 361, 1943.

206 Endicott, K. M., Kornberg, A., and Daft, F. S. Lesions in Rats Given Sulfathiazole, Sulfadiazine, Sulfanilamide, Sulfamerazine, Sulfapyrazine, or Acetylsulfadiazine in Purified Diets, *Pub. Health Rep.* **59** 49, 1944.

207 Totter, J. R., Shukers, C. F., and others. Studies on the Relation Between Vitamin M, Xanthopterin and Folic Acid, *J. Biol. Chem.* **152** 147, 1944.

208 Wright, L. D., and Welch, A. D. Folic Acid, Biotin and Pantothenic Acid Deficiency and Liver Storage of Various Vitamins in Rats Fed Succinylsulfathiazole in Highly Purified Rations, *J. Nutrition* **27** 55, 1944.

there may be either a deficiency of folic acid in the diet or perhaps a failure of the intestinal flora to synthesize folic acid, and hence the animal organism is deprived of the factor which controls the maturation of the white blood cells. While this theory is attractive and while there is evidence in favor of it, there are many gaps in the knowledge relating to this process which require further investigation.

It has been pointed out by Waisman and his associates<sup>209</sup> that young monkeys fail to grow and develop on a diet consisting of sucrose, purified casein, mineral salts, corn oil and cod liver oil, together with adequate levels of thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, choline, paraaminobenzoic acid, and  $\gamma$ -inositol. When such a diet was given to these animals there was a gradual loss of weight followed by a syndrome of anorexia, leukopenia, lowered resistance to secondary infections, increasing cachexia and death. They demonstrated further that the addition of liver extract, whole liver or "solubilized" liver to the synthetic diet caused a disappearance of all symptoms and that the animals showed striking gains in weight.

*Treatment of Agranulocytosis*—An important report is made by Smith, Cohen and Nichols<sup>210</sup> regarding the successful treatment of 2 patients with agranulocytosis with penicillin. They state that up to the time of their publication 1 case in which a similar treatment had been used had been cited<sup>211</sup>. In both the patients classic evidence of agranulocytosis developed after the administration of oxophenarsine hydrochloride (Mapharsen) for the treatment of syphilis. One patient received penicillin in doses of 20,000 Oxford units intramuscularly every three hours, beginning on the third day of the agranulocytosis. Sixteen hours after the first dose the temperature was normal, and the patient made a prompt recovery. A second patient was given penicillin therapy in a dosage of 10,000 units intramuscularly every three hours. Within thirty-eight hours he was afebrile. Although both patients received additional therapy, including blood transfusions, pentnucleotide and yellow

bone marrow, it is the opinion of the authors that the striking improvement which occurred during the first twenty-four hours of penicillin therapy warrant its further trial in the treatment of agranulocytosis. To us, the use of penicillin in the treatment of agranulocytosis seems to be logical, because it is the most effective agent available for the control of the sepsis which is the cause of death. Furthermore, penicillin is not responsible for the production of agranulocytosis or of any other untoward results.

The case of a gunner's mate, 24 years old, in whom agranulocytosis developed after the use of sulfathiazole is reported by Meredith, Douglas and Fink<sup>212</sup>. There are two points of interest in the paper. In the first place, the dangers of taking sulfonamide drugs indiscriminately are emphasized. For example, this patient two months before being seen by the authors had been ill for a week with jaundice and did not seek medical attention but took a total of 32 tablets (16 Gm) of sulfathiazole during the course of the illness. Four years before he had been uneventfully treated with sulfathiazole for gonorrhea and since that time had frequently taken smaller amounts for minor infections and venereal prophylaxis. The present illness began when the patient experienced the symptoms of a cold and on his own initiative took 12 tablets (6 Gm) of sulfathiazole during the day. The following day his throat was definitely sore, and that evening he had chills followed by fever. When seen at that time his white blood cell count was 2,700 per cubic millimeter, with a differential count of 56 per cent polymorphonuclear leukocytes, 40 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The following day the white blood cell count was 1,500 per cubic millimeter, with 100 per cent lymphocytes. The second point of interest is the use of large doses of penicillin as one form of treatment. When the diagnosis of agranulocytosis was established, intensive therapy was immediately instituted, consisting of transfusions of whole blood, intramuscular injections of liver extract, injections of pentnucleotide and the use of penicillin. The latter was administered in quantities of 100,000 units for the initial dose, 120,000 units during each of the following six days and then 90,000, 40,000 and 20,000 units on subsequent days. Penicillin therapy was discontinued on the eleventh day. In résumé, the therapy over a period of ten days was as follows: 2,500 cc of whole blood, 260 units of liver extract, 270 cc

209 Waisman, H. A., Rasmussen, A. F., Jr., Elvehjem, C. A., and Clark, P. F. Studies on Nutritional Requirements of Rhesus Monkey, *J. Nutrition* 26 205, 1943.

210 Smith, L. B., Cohen, F., and Nichols, R. G. Agranulocytosis Treated with Penicillin, *J. A. M. A.* 126 1027 (Dec 16) 1944.

211 Keefer, C. S., and others. Penicillin in the Treatment of Infections. Report of Five Hundred Cases, Statement by the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council, *J. A. M. A.* 122 1217 (Aug 28) 1943.

212 Meredith, W. C., Douglas, A. H. R., and Fink, H. Penicillin in Malignant Granulocytopenia. Report of Case, *U. S. Nav. M. Bull.* 43 1017, 1944.

of pentnucleotide and 970,000 Oxford units of penicillin. The patient made a complete recovery.

The case of a 22 year old seaman in whom agranulocytosis developed and who recovered after the use of penicillin is reported by Sprague and Ferguson<sup>213</sup>. This patient six months before had been treated for six weeks with a sulfonamide drug for gonorrhea. When observed by the authors, the patient again had received 36 Gm of sulfathiazole over a period of six days. At the end of this time fever developed, there was ulceration of the throat, and the white blood cell count was found to be 900 per cubic millimeter. It later fell to 275. The patient received many forms of treatment, including twenty-five blood transfusions of 250 cc each, pentnucleotide, yellow bone marrow and liver extract. In addition, penicillin was given in amounts of 20,000 units every four hours intramuscularly for five days. After this its use was discontinued and later resumed. A total dose of approximately 6,480,000 units was given, to which the authors attribute this person's recovery.

Pyridoxine was introduced in the treatment of leukopenia and granulocytopenia, according to Cantor and Scott,<sup>214</sup> for the following reasons. First, it had been shown that folic acid, a component of the vitamin B complex, is effective in preventing and curing the neutropenia produced in rats by the feeding of the insoluble sulfonamide compounds. Additional work has indicated that this effect is probably an indirect one, in the sense that the folic acid fed is required by coliform bacteria in the intestines for the production of some accessory substance, which, in turn, produces a granulocytic response. It has also been observed that microcytic hypochromic anemia produced in dogs by a deficiency of vitamin B<sub>6</sub> is not relieved by the administration of iron. Furthermore, the anemia of pellagra and pernicious anemia are similarly unresponsive to iron, while pyridoxine is a constituent of liver and yeast, both of which are effective in the treatment of these disorders. Also, it has been reported that the administration of pyridoxine intravenously to pellagrins

and to patients with pernicious anemia in a state of relapse results in improvement within forty-eight hours, with a striking increase in the leukocyte count, especially in the granulocytic series. Furthermore, they state that the administration of pyridoxine produces some benefit in persons with Cooley's anemia when it is used in association with chorionic gonadotropine. While all these observations may be true, it is not clear to us why pyridoxine should be of value in the treatment of leukopenia and granulocytopenia. The observers treated 3 patients with agranulocytic angina with a 10 per cent solution of pyridoxine hydrochloride in isotonic solution of sodium chloride in amounts totaling 125 mg to 200 mg intravenously daily. In 1 of these patients agranulocytic angina had developed after the administration of 4 Gm of sulfathiazole given over a period of twenty-four hours. There was no medication given to the second patient which could have been responsible for the agranulocytic angina except self-administered acetylsalicylic acid. The condition developed in the third patient after the use of thiouracil about two months after this therapy for hyperthyroidism was instituted. A total of 13.5 Gm of the drug had been taken. It is unusual, to say the least, that agranulocytic angina should develop in a patient who had received 4 Gm of sulfathiazole and also that the same condition should develop in a patient who had received only a total of 13.5 Gm of thiouracil over a period of two months. It is stated that the temperature of each patient fell to normal limits and that the symptoms disappeared promptly after the use of pyridoxine hydrochloride. These occurrences were associated with an increase in the number of leukocytes and the reappearance of granulocytes in the blood. Recovery followed in all patients. The observers conclude by stating that pyridoxine hydrochloride administered intravenously appears to be a useful agent for the treatment of agranulocytic angina of toxic origin. Its effectiveness in 3 instances suggests that pyridoxine acts by direct stimulation of the myelocytic elements in the bone marrow. No one can deny the possibility that pyridoxine hydrochloride may be effective in treating this disease. On the other hand, the recovery of 3 patients from a disease in which spontaneous recovery is not rare after the use of a drug for whose use there is no special logical basis does not place the claim on secure grounds.

213 Sprague, H. B., and Ferguson, L. K. Agranulocytosis Treated with Penicillin. Report of Case, U. S. Nav. M. Bull. **43** 1014, 1944.

214 Cantor, M. M., and Scott, J. W. Effect of Vitamin B<sub>6</sub> (Pyridoxine) in Treatment of Leukopenia and Granulocytopenia of Toxic Origin in Humans. Preliminary Report, Science **100** 545, 1944.

(To Be Continued)

## Book Reviews

**Constitution and Disease** By Julius Bauer, M D  
Price, \$4 Pp 247 New York Grune & Stratton,  
Inc, 1945

In this book Dr Bauer tries, one might say, to bridge the gap between pure genetics and clinical medicine. The general question of constitution is discussed from various aspects, with liberal allusion to practical examples. Obviously a discussion of this sort must be written from a somewhat personal point of view, and not every one will agree in all details with Dr Bauer's conclusions. From any standpoint, however, the book furnishes interesting and stimulating reading.

**Clinical Roentgenology of the Digestive Tract**  
By Maurice Feldman, M D, assistant professor of gastroenterology, University of Maryland. Second edition. Price, \$7 Pp 769, with 551 illustrations. Baltimore. Williams & Wilkins Company, 1945.

In *THE ARCHIVES* (53 1237 [June] 1939) was reviewed the first edition of this book, the reviewer commending the author on his complete and understanding presentation of such an extensive subject. The second edition is even more praiseworthy and, indeed, sets an unusual example in that it is shorter, cheaper and more extensively illustrated than was its predecessor. Most second editions do not follow such a pattern.

The text continues to present a thorough consideration of gastrointestinal disease which will interest both radiologist and clinician. The illustrations are admirable. The pertinent literature is extensively reviewed, and there is a short up-to-date bibliography at the end of each chapter. The present reviewer is glad to reaffirm in *THE ARCHIVES* that the book is an invaluable reference work and to predict for it continued success.

**Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy** By John A. Kolmer, M S, M D, Dr P H, Sc D, L L D, L H D, F A C P, professor of medicine in the School of Medicine and the School of Dentistry, Temple University, Director of the Research Institute of Cutaneous Medicine, formerly professor of pathology and bacteriology, Graduate School of Medicine, University of Pennsylvania. Cloth. Price not given. Pp 302, with 42 illustrations and tables. New York. D Appleton-Century Company, Inc, 1945.

This is a timely book and will interest practitioners of medicine from all branches. It represents the author's personal experience in the use of penicillin, together with a reasonably complete review of the work of other clinicians and investigators. It deals with the structure of penicillin and the method of its production and assay. It also describes the method of determining the concentration of penicillin in the blood, a procedure which is not generally carried out. The various methods of administration of penicillin are adequately dealt with, and a special section is included to cover the use of penicillin and its related substances in dentistry and oral surgery. In addition to penicillin, tyrothricin and gramicidin and some other substances that have come to be known as antibiotics are dis-

cussed. An appendix is included to care for matter that has come to the author's attention since the original manuscript was completed.

The book is a most interesting and valuable one. As with all books on new therapeutic agents, some of the statements in this book have already been modified by experience, but there is no detracting from the general value of the book on that account.

The bibliography and the list of references are excellent.

**The Specificity of Serological Reactions** By Karl Landsteiner, M D. Second revised edition. Price, \$5. Pp 310. Cambridge, Mass. Harvard University Press, 1945.

In 1936 the late Dr Landsteiner published the first edition of his now classic monographic review of serologic reactions. The advances of the subsequent years made a revision desirable, and the text was completed at the time of Dr Landsteiner's death, we are indebted to his son Ernest, also a physician, who undertook to see the revision carried through to the state of final publication.

This volume contains an excellent chapter on molecular structure and intermolecular forces, as they apply to immunologic reactions, contributed by Dr Linus Pauling. The remainder of the book includes an introductory section defining immunologic concepts and terminology and chapters on the serologic properties of various types of proteins, nonprotein cell substances and artificial conjugated antigens derived from simple chemical compounds, on cell antigens, on the nature and specificity of antibodies and on antigen-antibody reactions.

The enormous body of pertinent literature has been analyzed and built into a coherent concept of immunologic specificity by the worker whose wide-ranging intellect and personal contributions to fundamental research in the field made him uniquely fitted for the task. All who are interested in immunologic reactions are indebted to Dr Karl Landsteiner for this summary of his interpretation of the existing knowledge on the subject and will treasure the book as they do the memory of his scientific achievements.

**Publicaciones del centro investigaciones fisiológicas** Edited by Prof Roque A. Izzo, Director. Volume 7. Buenos Aires, Argentina. Pabellón "Las Provincias," Hospital Tornu, 1944.

Like the preceding six volumes, this (the seventh) volume of the collected studies of the Centro de Investigaciones fisiológicas consists of a group of papers and monographs on thoracic conditions. Although some of the work is of a high order, it would be expecting too much to have every study a classic. The monograph on constitution and tuberculosis is one of the best reviews on the subject and is supported by a worthy original study. There is little doubt left in the reader's mind that some genotypic (hereditary) aspects of constitution determine whether certain patients, such as the "heavy-set" and "elongated" types, present different reactions to the tubercle bacillus, with different prognoses. The former is found to have a

good prognosis and the latter a bad one, a distinction conforming to wide clinical experience. There are also different reactions in different races and ages of people to tuberculous infection, although the explanation offered for these reactions are sometimes inadequate and the authorities cited at no time present a majority opinion on any phase of the subject. The attempt to assign various "endocrine types of habitus" to special types of tuberculosis results in spreading the evidence rather thin. There is not due consideration of the possibilities of counterbalance of one or more of the many unfavorable characteristics by other more favorable characteristics.

A monograph on malformations of the lungs and bronchi is also complete and well presented, but the work has the tendency of other similar studies to fail to distinguish with certainty the acquired disease from true congenital cystic disease of the lung. Another article points out the necessity of performing tuberculin tests and examination of sputum in addition to roentgenographic examinations of the chest for the diagnosis of tuberculosis in children. Another, beautifully illustrated, article is devoted to the cervicothoracic diaphragm, or endothoracic fascia, covering the dome of the lungs. Still another study worthy of mention is one of pulmonary alveolar cells.

The paper and print are of the best. The illustrations are good in some articles and poor in others.

The volume is highly recommended for persons interested in pulmonary diseases.

**Diseases of the Nervous System in Infancy, Childhood and Adolescence.** By Frank R. Ford, M.D. Second edition. Cloth. Price, \$12.50. Pp. 1,143, with illustrations. Springfield, Ill. Charles C. Thomas, Publisher, 1944.

Dr. Ford allowed eight years to elapse before bringing out his present (second) edition, and it would require much more space to review in detail such an encyclopedic treatise. Features to be specially noted are the introductory chapters on the examination of the nervous system in general and the clinical aspects of the anatomy and physiology of the nervous system, the many excellent photographs and diagrams, the thorough bibliographies and the excellent general format with large readable type. Every variation of the complicated neurologic disorders of childhood is mentioned, as, for example, no less than forty-three hereditary and degenerative diseases. Prenatal diseases, infections, tumors and so forth present a hardly less formidable array. The illustrative case histories seem especially useful in dealing with material of this sort in which the nosologic aspect is so important. Dr. Ford's treatise will undoubtedly remain the standard reference work on the subject.

**Military Medical Manuals—A Manual of Tropical Medicine.** Prepared under the auspices of the Division of Medical Sciences of the National Research Council. Colonel Thomas T. Mackie, M.C., A.U.S., Major George W. Hunter III, Sn.C., A.U.S., and Captain C. Brooke Worth, M.C., A.U.S. Price, \$6. Pp. 727, with 284 illustrations. Philadelphia and London. W. B. Saunders Company, 1945.

Tropical medicine is a singular specialty because it is a conglomerate of sections from nearly all the medical and biologic sciences. Tropical medicine deals with the medical problems of the earth's equator. The physician in the tropics, therefore, must know something

of nearly everything, he must be protozoologist, bacteriologist, clinician, laboratory technician, hygienist, entomologist, chemist, expert in virus, rickettsial and metabolic diseases, helminthologist, drainage engineer, rat exterminator, administrator and surgeon. To provide him with a portable text dealing with these subjects in acceptable detail would be impossible. A manual, therefore, must limit itself to the most important topics likely to be required by the physicians actually in the tropics.

How well this manual has achieved its design to provide a concise and dependable source of old and new information is best comprehended by a careful study of the book. The numerous diseases and hazards of the tropics are presented briefly and clearly. The recommended treatments include the recent advances in medicine. Numerous instructive sketches and unusually clear illustrations illuminate the text. Many tables which condense parallel data are included. There are sections devoted to medically important arthropods and to medically important animals. Nutritional diseases and the effects of inadequate diets are discussed. Diagnostic laboratory procedures are carefully outlined. Finally, there is a generous index.

The manual kindled the enthusiasm of this reviewer. It is not only the best book of its kind, it is a combination of the good features of all the books of its kind. Here in one source the physician in the tropics can find practically everything he may need, presented in clear and authoritative fashion. The authors made use of all the sources available, as the long list of acknowledgments will prove, but the excellent condensation of this information is an achievement worthy of lavish praise. It is especially interesting to read of tsutsugamushi disease (scrub typhus) in New Guinea, of the uses of dimethylphthalate and of DDT in combating insects and of the usefulness of sulfonamide compounds in plague and dysenteries.

It is difficult to find something to criticize in this manual. One may wish that more had been said of the uses of penicillin in the treatment of certain infections, such as that caused by *Streptobacillus moniliformis*, for example. It would be valuable to present in a manual to be used in all countries tables of weights and measures, with instructions on how to convert Centigrade readings to Fahrenheit, inches to centimeters and liters to pints. Also, a brief glossary of terms, especially of the names given by the British to the common useful drugs, would be very helpful. But these are small matters. There are no typographic errors to be found, and the technical work of printing and binding is excellent. This manual is highly recommended to all who have an interest in tropical medicine. It will be found especially useful to medical students.

## News and Comment

### GENERAL NEWS

**The American College of Physicians**—The American College of Physicians will hold its annual meeting May 13-17, 1946 at the Philadelphia Municipal Auditorium, Thirty-Fourth Street below Spruce Street. Further information may be procured from the president, Dr. Ernest E. Irons, Chicago, or from the general chairman, Dr. George Morris Pierson, Philadelphia.

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